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Nivolumab (Addendum to Commission A15-27)[1]

Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum[2]:

- Helmut Hörn
- Katrin Nink
- Anke Schulz
- Beate Wieseler

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[2] Due to legal data protection regulations, employees have the right not to be named.

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Abbreviation	Meaning
AE	adverse event
BRAF	rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf)
BRAF V600 mut	BRAF V600 mutated
BRAF V600 wt	BRAF V600 wild type
CI_u	upper limit of confidence interval
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
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
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 24 November 2015 and on 1 December 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A15-27 (Nivolumab – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its written comments [2], the pharmaceutical company (hereinafter referred to as "the company") submitted supplementary information, which went beyond the information provided in the dossier, to prove the added benefit. This information particularly refers to analyses on adverse events (AEs) of the studies CA209-066 und CA209-067. The company presented these analyses because the analyses presented in the dossier [3] were rated as not interpretable in the dossier assessment. The reason for this was that a high proportion of the recorded events constituted progression of the underlying disease. The company also presented a new data cut-off for overall survival of the CA209-066 study (second data cut-off from 15 July 2015). The G-BA therefore commissioned IQWiG with the assessment of the additional analyses on AEs (research questions 1 and 2) and of the new data on overall survival (research question 2) presented by the company in its written comments, under consideration of the information provided in the dossier.

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

2 Assessment

2.1 Overview of the analyses subsequently submitted by the company

With its written comments, the company subsequently submitted a new data cut-off on overall survival in the CA209-066 study and further analyses on AEs in the studies CA209-066 and CA209-067 [2]. These data were dealt with as follows.

Data cut-off subsequently submitted

The analyses of the CA209-066 study (nivolumab versus dacarbazine) in the dossier for the early benefit assessment [1] contained all data up to the data cut-off on 24 June 2014 and therefore include only data unaffected by the unblinding and the treatment switching (allowed treatment switching from the dacarbazine arm to the nivolumab arm). After 24 June 2014, the double-blind, randomized part of the study was stopped, and the study was continued as an open-label extension phase.

In its written comments, the company presented a new data cut-off from the open-label extension phase. This data cut-off contained data on overall survival up to 15 July 2015. Hence the new data cut-off contained also data recorded after the unblinding and the corresponding possibility for treatment switching starting in July 2014. The company presented an analysis with censoring of the 27 patients with treatment switching and an analysis without it.

The new data cut-off contained no data on morbidity, health-related quality of life or AEs. Furthermore, neither subgroup analyses nor Kaplan-Meier curves were presented for overall survival.

The analysis with the data cut-off on 15 July 2015 was performed when, with 219 deaths, the number of deaths (218) was reached, after which an interim analysis of the study was planned according to the clinical study report (CSR).

Adverse events

The company presented further analyses on serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3, 4) and treatment discontinuations due to AEs for the studies CA209-066 (nivolumab versus dacarbazine) and CA209-067 (nivolumab versus ipilimumab) because the analyses presented in the dossier were rated as not interpretable. The reason for this was that a high proportion of the recorded events constituted progression of the underlying disease. For better readability, the original analyses of the company are hereinafter referred as “uncleansed analyses”, and the newly submitted analyses without consideration of the progression events as “cleansed analyses”.

In the cleansed analysis, the company excluded the events due to progression of the underlying disease and presented analyses with a follow-up period of 30 and 100 days on completion of the randomized study medication for the CA209-066 study, and analyses with a

follow-up period of 100 days on completion of the randomized study medication for the CA209-067 study.

In its comment, the company documented the Preferred Terms (PTs) included and excluded for the cleansing of the analyses. The choice of PTs and the company's approach appear plausible; the cleansed analyses presented are relevant for the assessment.

In the present addendum, the cleansed analyses with a follow-up period of 100 days on completion of the study medication were preferably used for the outcomes "SAEs" and "severe AEs (CTCAE grade 3, 4)". Deviating from this, the analyses with a shorter follow-up period were preferably used for the outcome "treatment discontinuation due to AEs" because a follow-up period after the end of the study medication is not meaningful for the outcome "discontinuation due to AEs".

The company presented no subgroup analyses for the cleansed AE analyses in its written comments. The similarity between the results of the analyses subsequently submitted and the analyses in Module 4 A of the dossier were investigated to check possible effect modifications. In case of sufficient similarity, the subgroup analyses based on the uncleansed data were used for conclusions on effect modification.

2.2 Research question 1: treatment-naive patients with BRAF V600 mut tumour

Research question 1 refers to treatment-naive patients with a rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf) (BRAF) V600 mutated (mut) tumour. The G-BA specified vemurafenib as ACT for this research question. Due to a lack of studies of direct comparisons, the company presented an indirect comparison of nivolumab versus vemurafenib using the common comparator dacarbazine in Module 4 A of the dossier, including the CA209-066 study with nivolumab and the BRIM 3 study with vemurafenib.

Similarity of the studies in the indirect comparison

As described in the benefit assessment, the indirect comparison is not usable particularly because the assumption of similarity as precondition for an indirect comparison was not fulfilled. This was shown in the proportion of patients with at least one SAE or with treatment discontinuation due to AEs in the respective dacarbazine arms, which differed notably.

The company argued in its written comments that the documentation of AEs caused by the underlying disease differed between the 2 studies. Whereas the investigators in the BRIM 3 study were required not to record progression of the underlying disease as AEs, even if this progression was rated as an SAE, the progressions rated as serious in the CA209-066 study were recorded as AEs. To account for this difference, the company presented cleansed analyses of the AEs, in which the events due to progression of the underlying disease were excluded, in its written comments (see Section 2.1). These analyses are compared in Table 1. This comparison shows that only a small part of the dissimilarity can be explained by the proportions of the patients with progression of the underlying disease, and that the large

differences between the dacarbazine arms in both studies persist even after cleansing of the data for progression events in the CA209-066 study. The cleansed analyses presented therefore did not result in a deviating assessment from the benefit assessment regarding the similarity of the studies BRIM 3 and CA209-066 and the suitability of the indirect comparison for the assessment of the added benefit. Hence there are still no usable data for the derivation of the added benefit of nivolumab in comparison with the ACT vemurafenib for treatment-naive patients with BRAF V600 mut melanoma.

Table 1: Examination of the assumption of similarity – RCT, indirect comparison: treatment-naive patients with BRAF V600 mut melanoma, nivolumab (patients with BRAF V600 wt melanoma) vs. vemurafenib (patients with BRAF V600 mut melanoma)

Outcome **Intervention** **Study**	**Nivolumab vs. vemurafenib**		**Dacarbazine**	
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**
SAEs				
Nivolumab				
CA209-066 uncleansed[a]	206	64 (31)	205	78 (38)
CA209-066 cleansed[b]	206	57 (28)	205	66 (32)
Vemurafenib				
BRIM3	336	110 (33)	282	45 (16)
Discontinuation due to AEs				
Nivolumab				
CA209-066 uncleansed[a]	206	14 (7)	205	24 (12)
CA209-066 cleansed[b]	206	11 (5)	205	20 (10)
Vemurafenib				
BRIM3	336	19 (6)	282	12 (4)

a: Including events due to progression of the underlying disease; follow-up 30 days after the end of the study medication (corresponding to follow-up time in the BRIM 3 study).
b: Without events due to progression of the underlying disease; follow-up 30 days after the end of the study medication (corresponding to follow-up time in the BRIM 3 study).
AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 mut: BRAF V600 mutated; BRAF V600 wt: BRAF V600 wild type; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.3 Research question 2: treatment-naive patients with BRAF V600 wt tumour

Research question 2 refers to treatment-naive patients with BRAF V600 wild type (wt) tumour. The G-BA specified dacarbazine and ipilimumab as ACT for this research question. In the dossier, the company derived the added benefit in comparison with dacarbazine as ACT and presented its CA209-067 study on the comparison of nivolumab with ipilimumab as supplementary information.

Following the benefit assessment [1], the relevant results from the documents subsequently submitted on the comparison of nivolumab with dacarbazine are presented below. The relevant results from the documents subsequently submitted on the comparison of nivolumab with ipilimumab can be found in Appendix B.

2.3.1 Risk of bias

The analysis on overall survival without censoring of the patients with treatment switching subsequently submitted by the company had a high risk of bias because 13% of the patients in the dacarbazine arm switched to the treatment of the nivolumab arm.

Due to the documents subsequently submitted, usable results on SAEs, treatment discontinuation due to AEs and severe AEs (CTCAE grade 3, 4) were now available. There was a high risk of bias for these outcomes because the observation period in the treatment arms differed notably [1], and was therefore possibly accompanied by informative censoring.

2.3.2 Results

Overall survival

The analysis of overall survival based on the data cut-off from 15 July 2015 without censoring of the patients with treatment switching subsequently submitted by the company had a high risk of bias and contained neither subgroup analyses, nor Kaplan-Meier curves, nor a description of the characteristics of the patients who switched treatment. However, since the data cut-off from 24 June 2014 presented in the dossier contained the complete analyses and was only based on data recorded before unblinding and treatment switching, this data cut-off was used for the benefit assessment. The data of the new data cut-off on 15 July 2015 are presented as additional information in Appendix A (Table 6). This analysis also showed a statistically significant advantage of nivolumab over dacarbazine.

Adverse events

Table 2 shows the cleansed analyses on AEs based on the data cut-off from 24 June 2014.

Table 2: Results subsequently submitted (cleansed AEs) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab vs. dacarbazine

Study Outcome category Outcome	Nivolumab N	Nivolumab Median time to event in months [95% CI] Patients with event n (%)	Dacarbazine N	Dacarbazine Median time to event in months [95% CI] Patients with event n (%)	Nivolumab vs. dacarbazine HR [95% CI][a]	Nivolumab vs. dacarbazine p-value[b]
CA209-066						
Adverse events						
AEs[c]	206	0.43 [0.30; 0.49] 193 (93.7)	205	0.10 [0.07; 0.20] 191 (93.2)	–	
SAEs[c]	206	NA [11.27; NA] 73 (35.4)	205	11.96 [7.33; NA] 80 (39.0)	0.72 [0.52; 0.99]	0.042
Treatment discontinuation due to AEs[d]	206	NA [NA; NA] 11 (5.3)	205	NA [NA; NA] 20 (9.8)	0.43 [0.20; 0.91]	0.023
Severe AEs (CTCAE grade 3, 4)[c]	206	13.57 [8.34; NA] 84 (40.8)	205	7.33 [5.45; NA] 93 (45.4)	0.70 [0.52; 0.94]	0.018

a: Cox model stratified by PD-L1 status and baseline metastasis.
b: Log-rank test stratified by PD-L1 status and baseline metastasis.
c: Without events due to progression of the underlying disease; follow-up 100 days after the end of the study medication.
d: Without events due to progression of the underlying disease; follow-up 30 days after the end of the study medication.
AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved or not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

There was a statistically significant difference in favour of nivolumab for each of the outcomes "SAEs", "treatment discontinuation due to AEs" and "severe AEs (CTCAE grade 3, 4)". This resulted in a hint of lesser harm from nivolumab in comparison with dacarbazine in each case.

Subgroups and other effect modifiers

The company presented no subgroup analyses of AEs in the documents subsequently submitted. On the one hand, the results of the cleansed and uncleansed analysis were not similar enough to transfer the results from the subgroup analyses of the uncleansed analysis to the cleansed analyses. On the other, no indications of relevant effect modifications for the outcomes on AEs could be identified from the subgroup analyses of the uncleansed analyses [3]. This concerns also the characteristic "sex", for which an indication of an effect modification for the outcome "overall survival" was identified. It was therefore assumed in the present situation that the cleansed analyses on AEs can be used for the total population.

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

2.3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit for AEs was estimated from the results subsequently submitted (see Table 3). In addition, the company subsequently submitted the exact upper limit of the confidence interval for overall survival for the subgroup of women with its written comments (data cut off: 24 June 2014). The upper limit provided in the dossier assessment was 0.95 and was therefore exactly on the border for the derivation of the extent of added benefit. The value subsequently submitted (CI_u: 0.9469) was below the limit of 0.95, however. This was considered for the derivation of the added benefit in the present addendum.

Table 3: Extent of added benefit at outcome level – treatment-naive patients with BRAF V600 wt tumour, nivolumab vs. dacarbazine

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab vs. dacarbazine** **Time to event** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival (data cut-off on 24 June 2014)		
Sex Men	Median: NA vs. 9.92 months HR 0.34 [0.22; 0.54] p < 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Women	Median: NA vs. 12.39 months HR 0.56 [0.33; 0.9469] p = 0.028 probability: "hint"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent "considerable"
Morbidity and health-related quality of life		
See dossier assessment	No usable data	Lesser benefit/added benefit not proven
Adverse events		
SAEs	Median: NA vs. 11.96 months HR: 0.72 [0.52; 0.99] p: 0.042 probability: "hint"	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1$ lesser harm, extent: "minor"
Treatment discontinuation due to AEs	Median: NA vs. NA months HR: 0.43 [0.20; 0.91] p: 0.023 probability: "hint"	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1$ lesser harm, extent: "minor"
Severe AEs (CTCAE grade 3, 4)	Median: 13.57 vs. 7.33 months HR: 0.70 [0.52; 0.94]; p: 0.018 probability: "hint"	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1$ lesser harm, extent: "minor"

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; NA: not applicable or not achieved; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 4 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 4: Positive and negative effects from the assessment of nivolumab in comparison with dacarbazine for treatment-naive patients with BRAF V600 wt tumour

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ Sex (men) indication of an added benefit – extent: “major” ▫ Sex (women) hint of an added benefit – extent: “considerable”	
Adverse events ▪ SAEs hint of lesser harm – extent: “minor” ▪ Treatment discontinuation due to AEs: hint of lesser harm – extent “minor” ▪ Severe AEs (CTCAE grade 3, 4) hint of lesser harm – extent: “minor”	
AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

Overall, only positive effects remain. Since there was an indication of an effect modification by the subgroup characteristic “sex” for the outcome “overall survival”, the overall assessment of added benefit was conducted separately for men and women.

Added benefit for men

For men, there was an indication of major added benefit for overall survival. Regarding AEs, there was a hint of lesser harm (extent: “minor”) for the total population in each case. There were still no usable data available for morbidity and health-related quality of life. Since the documents subsequently submitted now allowed balancing benefit and harm and there was lesser harm for AEs, in contrast to the dossier assessment, the extent of the added benefit was not downgraded but remained “major”.

Hence there is an indication of major added benefit of nivolumab in comparison with the ACT dacarbazine for treatment-naive men whose tumour is BRAF V600 mutation-negative.

Added benefit for women

For women, there was a hint of considerable added benefit for overall survival. Regarding AEs, there was a hint of lesser harm (extent: “minor”) in each case. There were still no usable data available for morbidity and health-related quality of life. Since the documents subsequently submitted now allowed balancing benefit and harm, there was lesser harm for AEs, and the upper limit of the confidence interval for overall survival was < 0.95 (according to the information provided in the written comments [2]), the extent of the added benefit was assessed as higher (i.e. “considerable”) than in the dossier assessment.

Hence there is a hint of considerable added benefit of nivolumab in comparison with the ACT dacarbazine for treatment-naive women whose tumour is BRAF V600 mutation-negative.

Summary

The result of the assessment of the added benefit of nivolumab in comparison with dacarbazine for treatment-naive patients with BRAF V600 wt tumour is presented in Table 5.

Table 5: Nivolumab – extent and probability of added benefit (research question 2)

Research question	**Therapeutic indication**	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
2	Treatment-naive patients with BRAF V600 mutation-negative tumour	**Dacarbazine** or ipilimumab[b]	Men	Indication of major added benefit
			Women	hint of considerable added benefit
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold. b: The company additionally investigated the research question on the comparison of nivolumab versus ipilimumab and presented it in Module 4 A and in its written comments as supplementary information. ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; G-BA: Federal Joint Committee				

3 References

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Appendix A – Supplementary presentation of overall survival in the CA209-066 study (research question 2)

Table 6: Results (overall survival, data cut-off on 15 July 2015 without censoring of patients who switched treatment) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab vs. dacarbazine

Study Outcome category Outcome	Nivolumab N	Nivolumab Median survival time in months [95% CI][a] Patients with event n (%)	Dacarbazine N	Dacarbazine Median survival time in months [95% CI][a] Patients with event n (%)	Nivolumab vs. dacarbazine HR [95% CI][b]	Nivolumab vs. dacarbazine p-value[c]
CA209-066						
Mortality						
Overall survival	210	NA [23.13; NA] 80 (38.1)	208	11.17 [9.56; 12.98] 139 (66.8)	0.43 [0.33; 0.57]	< 0.001

a: The 2-sided 95% CI was calculated with a log-log transformation (according to Brookmeyer and Crowley [4]).
b: Cox model stratified by PD-L1 status and baseline metastasis.
c: Log-rank test stratified by PD-L1 status and baseline metastasis.

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved or not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Appendix B – Supplementary presentation of the CA209-067 study for research question 2

The supplementary presentation refers to the comparison of nivolumab with ipilimumab in treatment-naive patients with a BRAF V600 wt tumour. For this purpose, the company presented a cleansed analysis on the outcomes of AEs (follow-up of 100 days) in its written comments. However, there were still no usable analyses on the outcomes mortality, morbidity and health-related quality of life. Balancing of positive and negative effects is therefore still not possible.

B.1 Results on added benefit

B.1.1 Risk of bias

Due to the documents subsequently submitted, usable results on SAEs, treatment discontinuations due to AEs and severe AEs (CTCAE grade 3, 4) were now available. There was a high risk of bias for these outcomes because the observation period in the treatment arms differed notably [1], and may therefore be accompanied by informative censoring.

B.1.2 Results

Table 7 summarizes the results on the comparison of nivolumab with ipilimumab. These consist of the cleansed analyses on AEs. For the other outcomes, there were neither usable data in Module 4 A [1], nor did the company present additional analyses in its written comments [2].

Table 7: Results (dichotomous outcomes) – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour: nivolumab vs. ipilimumab

Study Outcome category Outcome	Nivolumab N	Nivolumab Median time to event in months [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median time to event in months [95% CI] Patients with event n (%)	Nivolumab vs. ipilimumab HR [95% CI][a]	 p-value[b]
CA209-067						
Mortality						
Overall survival	No data available					
Morbidity						
Symptoms (EORTC QLQ-C30)	No usable data					
Health status (EQ-5D VAS)	No usable data					
Health-related quality of life						
EORTC QLQ-C30	No usable data					
Adverse events						
AEs[c]	215	0.39 [0.26; 0.49] 212 (98.6)	215	0.36 [0.30; 0.46] 213 (99.1)	–	
SAEs[c]	215	NA [14.23; NA] 74 (34.4)	215	5.95 [4.50; 12.65] 111 (51.6)	0.53 [0.39; 0.71]	< 0.001
Treatment discontinuation due to AEs[c]	215	NA [NA; NA] 24 (11.2)	215	NA [NA; NA] 38 (17.7)	0.55 [0.33; 0.91]	0.020
Severe AEs (CTCAE grade 3, 4)[c]	215	13.04 [7.49; NA] 100 (46.5)	215	4.30 [2.79; 6.18] 128 (59.5)	0.62 [0.48; 0.81]	< 0.001

a: Cox model stratified by PD-L1 status and baseline metastasis.
b: Log-rank test stratified by PD-L1 status and baseline metastasis.
c: Without events due to progression of the underlying disease; follow-up 100 days after the end of the study medication.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved or not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Adverse events

There was a statistically significant difference in favour of nivolumab for each of the outcomes “SAEs”, “treatment discontinuation due to AEs” and “severe AEs (CTCAE grade 3, 4)”. This resulted in a hint of lesser harm from nivolumab in comparison with ipilimumab in each case.

Subgroups and other effect modifiers

The company presented no subgroup analyses for the cleansed AEs in its analyses subsequently submitted. Since the results of the cleansed survival time analyses with a follow-up of 100 days subsequently submitted hardly differed from the uncleansed survival time analyses with a follow-up of 30 days presented in Module 4 A of the dossier [3], the subgroup analyses based on the uncleansed analyses with a follow-up of 30 days from Module 4 A were considered as an auxiliary measure in the investigation of subgroups and other effect modifiers.

Of the potential effect modifiers included in the benefit assessment, proof of an interaction ($p < 0.05$) in SAEs, and an indication of an interaction ($0.05 \leq p < 0.20$) in treatment discontinuation due to AEs and in severe AEs (CTCAE grade 3, 4) were shown for sex (see Table 8). There was lesser harm of nivolumab in comparison with ipilimumab only for men, whereas the difference between the 2 treatment arms for women was not statistically significant in any of the 3 outcomes on AEs.

Table 8: Subgroups (uncleansed AEs, 30 days follow-up) – RCT, direct comparison: treatment-naive patients with BRAF V600 wt tumour: nivolumab vs. ipilimumab

Study Outcome Characteristic Subgroup	Nivolumab N	Nivolumab Median time to event in months [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median time to event in months [95% CI] Patients with event n (%)	Nivolumab vs. ipilimumab HR [95% CI][a]	Nivolumab vs. ipilimumab p-value[b]
Study CA209-067						
SAEs						
Sex						
Men	139	15.54 [14.23; NA] 48 (34.5)	142	4.24 [2.92; 5.75] 83 (58.5)	0.40 [0.28; 0.58]	< 0.001
Women	76	11.99 [6.70; NA] 30 (39.5)	73	NA [3.32; NA] 31 (42.5)	0.85 [0.52; 1.41]	0.532
					Interaction:	0.019[c]
Treatment discontinuation due to AEs						
Sex						
Men	139	NA [NA; NA] 16 (11.5)	142	NA [NA; NA] 32 (22.5)	0.42 [0.23; 0.77]	0.004
Women	76	NA [13.37; NA] 13 (17.1)	73	NA [NA; NA] 13 (17.8)	0.84 [0.39; 1.82]	0.665
					Interaction:	0.110[c]
Severe AEs (CTCAE grade 3, 4)						
Sex						
Men	139	13.08 [7.52; NA] 63 (45.3)	142	2.99 [2.00; 5.09] 90 (63.4)	0.49 [0.35; 0.68]	< 0.001
Women	76	8.77 [4.76; NA] 35 (46.1)	73	5.16 [2.86; NA] 37 (50.7)	0.84 [0.53; 1.34]	0.466
					Interaction:	0.063[c]

a: Unstratified Cox model.
b: Unstratified log-rank test; exceptions are provided.
c: From Cox model with interaction term treatment group*subgroup characteristic.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved or not calculable; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

B.1.3 Conclusions

The additional analyses of AEs presented by the company in its written comments showed a hint of lesser harm of nivolumab in comparison with ipilimumab in SAEs, treatment discontinuation due to AEs, and severe AEs (CTCAE grade 3, 4). Based on the uncleansed subgroup analyses presented in the dossier, this lesser harm was only found for men, whereas there was no hint of greater or lesser harm for these outcomes for women. Since there were still no results for the side of benefit, no balancing of positive and negative effects can be conducted.