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Nivolumab (melanoma) –

Addendum to Commission A16-35[1]

Addendum

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Abbreviation	Meaning
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
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
RCT	randomized controlled trial
SAE	serious adverse event
SOC	System Organ Class

1 Background

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

In Module 4 E [2] of its dossier on nivolumab, the pharmaceutical company (hereinafter referred to as "the company") had presented the studies CA209-067 and CA209-069 for research question 2 of the dossier assessment (treatment-naive patients with B-Raf [rapidly accelerated fibrosarcoma – isoform B] [BRAF] V600 wild type [wt] tumour). It presented analyses on the outcome "overall survival" for the 18-month data cut-off of the CA209-067 study and for the 24-month data cut-off of the CA209-069 study. Complete analyses on further patient-relevant outcomes, specifically on side effects, were only available for the early data cut-offs of both studies (9-month data cut-off of the CA209-067 study and 6-month data cut-off of the CA209-069 study), however. Hence the extent of side effects was subject to high uncertainty in dossier assessment A16-35 [1]. As a consequence, the certainty of conclusions of the result was downgraded.

In its written comments to the dossier assessment [3] and after the oral hearing, the company sent supplementary information, which went beyond the information provided in the dossier on nivolumab [2], to prove the added benefit. The G-BA therefore commissioned IQWiG with further assessments.

The G-BA's commission specifically addressed the assessment of the data cut-off of study CA209-069 after 24 months and the analysis of the data on specific adverse events (AEs) in study CA209-067 provided by the company after the oral hearing.

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

2 Assessment

With its comment and after the oral hearing, the company presented further analyses of the studies CA209-067 and CA209-069 [4,5]. The data subsequently submitted are assessed in Section 2.1. Section 2.2 contains the conclusions on the extent and probability of the added benefit of nivolumab under consideration of dossier assessment A16-35 and of the data assessed in the present addendum.

2.1 Results

Underlying data

Table 1 provides an overview of the data subsequently submitted by the company.

Table 1: Overview of the analyses of the studies CA209-067 and CA209-069 subsequently submitted, treatment-naive patients with BRAF V600 wt tumour

Study	**Outcomes**[a]			
Data cut-off	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade 3-4)**	**Specific AEs**
CA209-067 (N = 431)				
17 Feb 2015 (9 months)	Yes	Yes	Yes	**Yes**
10 Nov 2015 (18 months)	No	No	No	No
13 Sep 2016 (28 months)	No	No	No	No
CA209-069 (N = 109)				
4 Sep 2014 (6 months)	Yes	Yes	Yes	Yes
30 Jan 2015 (12 months)	No	No	No	No
25 Feb 2016 (24 months)	**Yes**	**Yes**	**Yes**	**Yes**

a: The data presented in the commenting procedure and after the oral hearing are printed in bold.

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; N: number of randomized patients; SAE: serious adverse event

For the CA209-067 study, the company presented AE data by System Organ Class (SOC) and Preferred Term (PT) for the population of BRAF V600 wt patients for the data cut-off on 17 February 2015 (9 months). The analyses presented were used for the presentation of common and specific AEs.

In addition, the company presented AE analyses of the CA209-067 study after at least 28 months of follow-up (data cut-off on 13 September 2016). These were analyses of the total population of the study, however; analyses of the relevant subpopulation of BRAF V600 wt patients were not available. Hence the 28-month data of the larger study could not be used for the assessment.

For the CA209-069 study, the company presented analyses of side effects (overall rates and AE data by SOC and PT) for the data cut-off after 24 months (data cut-off on 25 February 2016). These can be used for the assessment because they were analyses of the relevant subpopulation (patients with BRAF V600 wt tumour) of the study.

Under consideration of the available data, a meta-analysis of the side effects at the later data cut-offs of the studies CA209-067 (28 months) and CA209-069 (24 months) is not possible. Hence, as in the dossier assessment, no conclusions can be drawn on the extent of side effects over the total study period.

A meta-analysis of specific AEs was conducted on the basis of the AE data by SOC and PT for the population of BRAF V600 wt patients for the data cut-off from 17 February 2015 (9 months) of the CA209-067 study and for the data cut-off from 4 September 2014 (6 months) of the CA209-069 study. Analyses of the specific AEs on the basis of the data cut-off of the CA209-069 study after 24 months are presented as additional information.

The analyses of the overall rates of serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4) and discontinuations due to AEs in the CA209-069 study after 24 months are presented as additional information to the meta-analyses of these outcomes already shown in dossier assessment A16-35 [1].

Tables with the overviews of the most common AEs are presented in Appendix A.

Risk of bias

The risk of bias for all outcomes on side effects was rated as high. See dossier assessment A16-35 for reasons [1].

Results on specific adverse events from the early data cut-offs of the studies CA209-067 and CA209-069

The presentation of specific AEs deviates from dossier assessment A16-35 [1]. The reason for this is that the choice of specific AEs for the present report was conducted on a broader basis of data in comparison with dossier assessment A16-35 (AE data by SOC and PT for the studies CA209-067 and CA209-069 at the 9- and 6-month data cut-off).

Table 2 shows the results on specific AEs.

Table 2: Results (specific AEs) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour, nivolumab + ipilimumab vs. ipilimumab (9- and 6-month data cut-off)

Outcome category Outcome Study	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Patients with event n (%)	Ipilimumab N	Ipilimumab Patients with event n (%)	Nivolumab + ipilimumab vs. ipilimumab RR [95% CI][a]; p-value[b]
Side effects[c, d]					
Vomiting (PT, AEs)					
CA209-067	212	59 (27.8)	215	34 (15.8)	1.76 [1.21; 2.57]
CA209-069	71	13 (18.3)	37	5 (13.5)	1.35 [0.52; 3.51]
Total[e]					1.70 [1.20; 2.41]; 0.003
Endocrine disorders (SOC, SAEs)					
CA209-067	212	20 (9.4)	215	7 (3.3)	2.90 [1.25; 6.71]
CA209-069	71	3 (4.2)	37	1 (2.7)	1.56 [0.17; 14.51]
Total[e]					2.68 [1.22; 5.89]; 0.014
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)					
CA209-067	212	20 (9.4)	215	8 (3.7)	2.54 [1.14; 5.63]
CA209-069	71	7 (9.9)	37	3 (8.1)	1.22 [0.33; 4.43]
Total[e]					2.07 [1.05; 4.08]; 0.036
Hepatobiliary disorders (SOC, SAEs)					
CA209-067	212	17 (8.0)	215	4 (1.9)	4.31 [1.47; 12.60]
CA209-069	71	2 (2.8)	37	0 (0)	2.64 [0.13; 53.58]
Total[e]					4.08 [1.48; 11.20]; 0.006
Fatigue (PT, severe AEs [CTCAE grade 3-4])					
CA209-067	212	12 (5.7)	215	3 (1.4)	4.06 [1.16; 14.17]
CA209-069	71	5 (7.0)	37	1 (2.7)	2.61 [0.32; 21.49]
Total[e]					3.62 [1.23; 10.60]; 0.019
Skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade 3–4])					
CA209-067	212	16 (7.5)	215	6 (2.8)	2.70 [1.08; 6.78]
CA209-069	71	8 (11.3)	37	0 (0)	8.97 [0.53; 151.27]
Total[e]					3.03 [1.27; 7.27]; 0.013
Eye disorders (SOC, AEs)					
CA209-067		ND		ND	ND
CA209-069	71	17 (23.9)	37	2 (5.4)	4.43 [1.08; 18.15]; 0.017

(continued)

Table 2: Results (specific AEs) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour, nivolumab + ipilimumab vs. ipilimumab (9- and 6-month data cut-off) (continued)

a: RR and CI: Institute's calculation.
b: Institute's calculation, unconditional exact test (CSZ method according to [6]).
c: Information with 30 days of follow-up after treatment discontinuation.
d: Information for the data cut-off on 17 February 2015 (after 9 months) for study CA209-067 and on 4 September 2014 (after 6 months) for study CA209-069.
e: Institute's calculation from meta-analysis.
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; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The meta-analyses of the studies CA209-067 and CA209-069 showed a statistically significant difference to the disadvantage of nivolumab + ipilimumab for the following outcomes:

- vomiting (PT, AEs)
- endocrine disorders (SOC, SAEs)
- respiratory, thoracic and mediastinal disorders (SOC, SAEs)
- hepatobiliary disorders (SOC, SAEs)
- fatigue (PT, severe AEs [CTCAE grade 3-4])
- skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade 3–4])

Since the risk of bias for each of these outcomes was rated as high, this resulted in an indication of greater harm from nivolumab + ipilimumab in comparison with ipilimumab for each of these outcomes. Data for the outcome "eye disorders" (SOC, AEs) were only available from study CA209-069. A statistically significant difference to the disadvantage of nivolumab + ipilimumab was shown. Since the risk of bias for this outcome was also rated as high, this resulted in a hint of greater harm from nivolumab + ipilimumab in comparison with ipilimumab.

Supplementary presentation of the analyses of the side effects of study CA209-069 after 24 months

Table 3 and Table 4 provide a supplementary presentation of the side effects in the CA209-069 study after 24 months.

Table 3: Results (side effects, supplementary presentation) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour, nivolumab + ipilimumab vs. ipilimumab (study CA209-069, 24-month data cut-off)

Outcome category **Outcome** **Study**	**Nivolumab + ipilimumab**		**Ipilimumab**		**Nivolumab + ipilimumab vs. ipilimumab**
	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**
Side effects[a, b]					
AEs (supplementary information)					
CA209-069	71	0.13 [0.07; 0.23] 71 (100)	37	0.20 [0.07; 0.39] 37 (100.0)	–
SAEs					
CA209-069	71	2.60 [1.77; 4.40] 48 (67.6)	37	7.62 [2.86; NA] 21 (56.8)	1.41 [0.84; 2.37]; 0.187
Severe AEs (CTCAE grade 3–4)					
CA209-069	71	1.81 [1.41; 2.69] 58 (81.7)	37	4.11 [2.37; 15.61] 24 (64.9)	1.82 [1.12; 2.93]; 0.013
Discontinuation due to AEs					
CA209-069	71	5.29 [3.06; NA] 32 (45.1)	37	NA [NA; NA] 3 (8.1)	6.59 [2.02; 21.51]; < 0.001

a: AEs up to 100 days after the end of treatment except treatment discontinuation due to AEs (up to 30 days after the end of treatment), without events associated with the underlying disease.
b: AEs at the data cut-off 25 February 2016 (24-month data cut-off).

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; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 4: Results (specific AEs, supplementary presentation) – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour, nivolumab + ipilimumab vs. ipilimumab (study CA209-069, 24-month data cut-off)

Outcome category Outcome Study	Nivolumab + ipilimumab		Ipilimumab		Nivolumab + ipilimumab vs. ipilimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p-value[b]
Side effects[c, d]					
Vomiting (PT, AEs)	71	17 (23.9)	37	7 (18.9)	1.27 [0.58; 2.78]; 0.613
Endocrine disorders (SOC, SAEs)	71	3 (4.2)	37	1 (2.7)	1.56 [0.17; 14.51]; 0.790
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	71	8 (11.3)	37	3 (8.1)	1.39 [0.39; 4.93]; 0.626
Hepatobiliary disorders (SOC, SAEs)	71	2 (2.8)	37	0 (0)	2.64 [0.13; 53.58]; 0.404
Fatigue (PT, severe AEs [CTCAE grade 3-4])	71	5 (7.0)	37	1 (2.7)	2.61 [0.32; 21.49]; 0.418
Skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade 3–4])	71	9 (12.7)	37	0 (0)	10.03 [0.60; 167.65]; 0.025
Eye disorders (SOC, AEs)	71	20 (28.2)	37	2 (5.4)	5.21 [1.29; 21.09]; 0.005

a: RR and CI: Institute's calculation.
b: Institute's calculation, unconditional exact test (CSZ method according to [6]).
c: Information with 30 days of follow-up after treatment discontinuation.
d: Information for the data cut-off from 25 February 2016 (after 24 months) for the CA209-069 study.
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; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The analyses of the data cut-off of the CA209-069 study after 24 months showed that the results on the outcomes "SAEs", "severe AEs" (CTCAE grade 3–4) and "discontinuation due to AEs" are consistent with those of dossier assessment A16-35 [1] and therefore confirm the overall conclusion on these outcomes. As in the meta-analysis of the early assessment, a direction of the effect to the disadvantage of nivolumab + ipilimumab was shown for specific AEs in each case. However, the effect in the individual study was only statistically significant for the outcomes "skin and subcutaneous tissue disorders""(SOC, severe AEs [CTCAE grade 3–4]) and "eye disorders" (SOC, AEs).

2.2 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented in the following Table 5 for the outcomes on specific AEs at outcome level. The methods used for this purpose are explained in the *General Methods* of IQWiG [7].

Table 5: Extent of added benefit at outcome level – treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab (9- and 6-month data cut-off)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. ipilimumab** **Proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Vomiting (PT, AEs)	18.3% to 27.8% vs. 13.5% to 15.8% RR: 1.70 [1.20; 2.41] RR: 0.59 [0.41; 0.83][c] p = 0.003 probability: "indication"	Outcome category: non-serious/non-severe side effects $0.8 \leq CI_u < 0.9$ greater harm, extent: "minor"
Endocrine disorders (SOC, SAEs)	4.2% to 9.4% vs. 2.7% to 3.3% RR: 2.68 [1.22; 5.89] RR: 0.37 [0.17; 0.82][c] p = 0.014 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	9.4% to 9.9% vs. 3.7% to 8.1% RR: 2.07 [1.05; 4.08] RR: 0.48 [0.25; 0.95][c] p = 0.036 probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Hepatobiliary disorders (SOC, SAEs)	2.8% to 8.0% vs. 0% to 1.9% RR: 4.08 [1.48; 11.20] RR: 0.25 [0.09; 0.68][c] p = 0.006 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk $\geq 5\%$ greater harm, extent: "major"
Fatigue (PT, severe AEs [CTCAE grade 3-4])	5.7% to 7.0% vs. 1.4% to 2.7% RR: 3.62 [1.23; 10.60] RR: 0.28 [0.09; 0.81][c] p = 0.019 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade 3–4])	7.5% to 11.3% vs. 0% to 2.8% RR: 3.03 [1.27; 7.27]; RR: 0.33 [0.14; 0.79][c] p = 0.013 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"

(continued)

Table 5: Extent of added benefit at outcome level – treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab (9- and 6-month data cut-off) (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 CIu.
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
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 confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; NA: not achieved; NC: not calculated; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

The following Table 6 shows the positive and negative effects of nivolumab + ipilimumab versus ipilimumab under consideration of the results of dossier assessment A16-35 and of the present addendum. Changes resulting from the present addendum are presented in italics.

Table 6: Positive and negative effects from the assessment of nivolumab + ipilimumab in comparison with ipilimumab for treatment-naive patients with BRAF V600 wt tumour

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ Men proof of an added benefit – extent: "major" ▫ Women indication of an added benefit – extent: "non-quantifiable"	
	Morbidity[a] ▪ Symptoms (EORTC QLQ-C30) ▫ Nausea and vomiting - Metastases at the start of the study, M0/M1a/M1b: hint of lesser benefit – extent: "minor**"**
Health-related quality of life[a] ▪ Functional scales of the EORTC (QLQ-C30) ▫ Physical functioning - metastases at the start of the study, M1c: hint of an added benefit – extent: "minor**"**	Health-related quality of life[a] ▪ Functional scales of the EORTC (QLQ-C30) ▫ Cognitive functioning: hint of lesser benefit – extent: "minor" ▫ Global health status - metastases at the start of the study, M0/M1a/M1b: hint of lesser benefit – extent: "considerable**"**
	Serious/severe side effects ▪ SAEs: indication of greater harm – extent: "major" ▪ Severe AEs (CTCAE grade 3-4) ▫ metastases at the start of the study, M0/M1a/M1b: indication of greater harm – extent: "major" ▪ *Endocrine disorders (SOC, SAEs): indication of greater harm – extent: "considerable"* ▪ *Respiratory, thoracic and mediastinal disorders (SOC, SAEs): indication of greater harm – extent: "minor"* ▪ *Hepatobiliary disorders (SOC, SAEs): indication of greater harm – extent: "major"* ▪ *Fatigue (PT, severe AEs [CTCAE grade 3–4]): indication of greater harm – extent: "considerable"* ▪ *Skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade 3–4]): indication of greater harm – extent: "considerable"*
	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: indication of greater harm – extent: "non-quantifiable" ▪ *Vomiting (PT, AEs): indication of greater harm – extent: "minor"*

a: Only data from the CA209-067 study were available.

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; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class

In comparison with dossier assessment A16-35, there were indications of additional negative effects with a maximum extent of “major”. Hence the results of dossier assessment A16-35 were largely confirmed, which had also shown greater harm of major extent. Conclusions on side effects over the total study period of both studies are still not possible because no analyses for the relevant subpopulation were available at the data cut-off from 13 September 2016 (28 months) of study CA209-067. The conclusion of dossier assessment A16-35 has not changed: There is an indication of considerable added benefit for men with advanced (unresectable or metastatic) treatment-naive BRAF V600 wt melanoma. There is a hint of a non-quantifiable added benefit, which can be at most “considerable”, for women with advanced (unresectable or metastatic) treatment-naive BRAF V600 wt melanoma.

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Appendix A – Results on side effects

Table 7: Common AEs (≥ 10% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-067 (9-month data cut-off)

Study	Patients with event n (%)	
SOC[a] PT[a]	Nivolumab + ipilimumab N = 212	Ipilimumab N = 215
Study CA209-067 (data cut-off from 17 February 2015, 9 months)		
Overall rate of AEs[b]	211 (99.5)	213 (99.1)
Gastrointestinal disorders	161 (75.9)	164 (76.3)
Diarrhoea	103 (48.6)	101 (47.0)
Nausea	81 (38.2)	52 (24.2)
Vomiting	59 (27.8)	34 (15.8)
Constipation	42 (19.8)	45 (20.9)
Abdominal pain	30 (14.2)	38 (17.7)
Colitis	28 (13.2)	27 (12.6)
General disorders and administration site conditions	167 (78.8)	149 (69.3)
Fatigue	102 (48.1)	93 (43.3)
Fever	70 (33.0)	37 (17.2)
Asthenia	31 (14.6)	19 (8.8)
Oedema peripheral	22 (10.4)	22 (10.2)
Skin and subcutaneous tissue disorders	146 (68.9)	145 (67.4)
Pruritus	73 (34.4)	96 (44.7)
Rash	67 (31.6)	48 (22.3)
Rash maculo-papular	23 (10.8)	30 (14.0)
Musculoskeletal and connective tissue disorders	96 (45.3)	94 (43.7)
Arthralgia	39 (18.4)	33 (15.3)
Back pain	20 (9.4)	28 (13.0)
Respiratory, thoracic and mediastinal disorders	99 (46.7)	88 (40.9)
Cough	44 (20.8)	42 (19.5)
Dyspnoea	44 (20.8)	32 (14.9)
Infections and infestations	98 (46.2)	83 (38.6)
Nervous system disorders	89 (42.0)	88 (40.9)
Headache	44 (20.8)	40 (18.6)
Dizziness	23 (10.8)	18 (8.4)
Investigations	106 (50.0)	69 (32.1)
Alanine aminotransferase increased	40 (18.9)	12 (5.6)
Aspartate aminotransferase increased	38 (17.9)	13 (6.0)
Lipase increased	29 (13.7)	17 (7.9)
Weight decreased	25 (11.8)	12 (5.6)

(continued)

Table 7: Common AEs (≥ 10% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-067 (9-month data cut-off) (continued)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Nivolumab + ipilimumab N = 212**	**Ipilimumab N = 215**
Metabolism and nutrition disorders	90 (42.5)	76 (35.3)
Decreased appetite	57 (26.9)	46 (21.4)
Psychiatric disorders	47 (22.2)	51 (23.7)
Insomnia	25 (11.8)	31 (14.4)
Endocrine disorders	64 (30.2)	20 (9.3)
Hypothyroidism	34 (16.0)	8 (3.7)
Vascular disorders	42 (19.8)	36 (16.7)
Blood and lymphatic system disorders	34 (16.0)	37 (17.2)
Anaemia	18 (8.5)	29 (13.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22 (10.4)	35 (16.3)
Malignant neoplasm progression	10 (4.7)	22 (10.2)

a: MedDRA version 17.1; SOC and PT designations taken from MedDRA without adaptation.
b: The events associated with progression were not excluded.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 8: Common SAEs (≥ 5% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-067 (9-month data cut-off)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Nivolumab + ipilimumab N = 212**	**Ipilimumab N = 215**
Study CA209-067 (data cut-off from 17 February 2015, 9 months)		
Overall rate of SAEs[b]	148 (69.8)	114 (53.0)
Gastrointestinal disorders	56 (26.4)	47 (21.9)
Colitis	23 (10.8)	21 (9.8)
Diarrhoea	22 (10.4)	18 (8.4)
General disorders and administration site conditions	32 (15.1)	11 (5.1)
Fever	13 (6.1)	5 (2.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (5.2)	28 (13.0)
Malignant neoplasm progression	8 (3.8)	20 (9.3)
Infections and infestations	18 (8.5)	16 (7.4)
Respiratory, thoracic and mediastinal disorders	20 (9.4)	8 (3.7)
Endocrine disorders	20 (9.4)	7 (3.3)
Hepatobiliary disorders	17 (8.0)	4 (1.9)
Metabolism and nutrition disorders	13 (6.1)	5 (2.3)
Renal and urinary disorders	13 (6.1)	5 (2.3)

a: MedDRA version 17.1; SOC and PT designations taken from MedDRA without adaptation.
b: The events associated with progression were not excluded.

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 9: Common severe AEs with CTCAE grade 3–4 (≥ 5% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-067 (9-month data cut-off)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Nivolumab + ipilimumab** **N = 212**	**Ipilimumab** **N = 215**
Study CA209-067 (data cut-off from 17 February 2015, 9 months)		
Overall rate of AEs with CTCAE grade 3–4[b]	146 (68.9)	122 (56.7)
Gastrointestinal disorders	46 (21.7)	47 (21.9)
Diarrhoea	20 (9.4)	20 (9.3)
Colitis	18 (8.5)	19 (8.8)
General disorders and administration site conditions	23 (10.8)	13 (6.0)
Fatigue	12 (5.7)	3 (1.4)
Skin and subcutaneous tissue disorders	16 (7.5)	6 (2.8)
Respiratory, thoracic and mediastinal disorders	19 (9.0)	6 (2.8)
Infections and infestations	21 (9.9)	17 (7.9)
Nervous system disorders	12 (5.7)	11 (5.1)
Investigations	62 (29.2)	26 (12.1)
Alanine aminotransferase increased	19 (9.0)	6 (2.8)
Aspartate aminotransferase increased	16 (7.5)	4 (1.9)
Lipase increased	24 (11.3)	11 (5.1)
Metabolism and nutrition disorders	21 (9.9)	20 (9.3)
Endocrine disorders	14 (6.6)	7 (3.3)
Blood and lymphatic system disorders	5 (2.4)	14 (6.5)
Anaemia	4 (1.9)	13 (6.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (2.4)	19 (8.8)
Malignant neoplasm progression	1 (0.5)	12 (5.6)

a: MedDRA version 17.1; SOC and PT designations taken from MedDRA without adaptation.
b: The events associated with progression were not excluded.

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; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 10: Common discontinuations due to AEs (≥ 2% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-067 (9-month data cut-off)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Nivolumab + ipilimumab N = 212**	**Ipilimumab N = 215**
Study CA209-067 (data cut-off from 17 February 2015, 9 months)		
Overall rate of discontinuations due to AEs[b]	87 (41.0)	45 (20.9)
Gastrointestinal disorders	33 (15.6)	28 (13.0)
Colitis	20 (9.4)	17 (7.9)
Diarrhoea	14 (6.6)	12 (5.6)
Investigations	20 (9.4)	2 (0.9)
Alanine aminotransferase increased	9 (4.2)	2 (0.9)
Aspartate aminotransferase increased	9 (4.2)	2 (0.9)
Transaminases increased	5 (2.4)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.4)	9 (4.2)
Malignant neoplasm progression	2 (0.9)	6 (2.8)
Respiratory, thoracic and mediastinal disorders	9 (4.2)	0 (0)
Hepatobiliary disorders	6 (2.8)	1 (0.5)

a: MedDRA version 17.1; SOC and PT designations taken from MedDRA without adaptation.
b: The events associated with progression were not excluded.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 11: Common AEs (≥ 10% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-069 (24-month data cut-off)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Nivolumab + ipilimumab** **N = 71**	**Ipilimumab** **N = 37**
Study CA209-069 (data cut-off from 25 February 2016, 24 months)		
Overall rate of AEs[b]	71 (100)	37 (100)
General disorders and administration site conditions	61 (85.9)	33 (89.2)
Fatigue	46 (64.8)	26 (70.3)
Fever	21 (29.6)	12 (32.4)
Chills	17 (23.9)	6 (16.2)
Oedema peripheral	13 (18.3)	8 (21.6)
Asthenia	9 (12.7)	6 (16.2)
Pain	9 (12.7)	6 (16.2)
Chest pain	5 (7.0)	5 (13.5)
Mucosal inflammation	3 (4.2)	4 (10.8)
Gastrointestinal disorders	56 (78.9)	33 (89.2)
Diarrhoea	41 (57.7)	20 (54.1)
Nausea	24 (33.8)	16 (43.2)
Constipation	19 (26.8)	12 (32.4)
Vomiting	17 (23.9)	7 (18.9)
Abdominal pain	14 (19.7)	9 (24.3)
Colitis	15 (21.1)	3 (8.1)
Upper abdominal pain	4 (5.6)	4 (10.8)
Flatulence	2 (2.8)	4 (10.8)
Rectal haemorrhage	1 (1.4)	4 (10.8)
Skin and subcutaneous tissue disorders	59 (83.1)	28 (75.7)
Pruritus	34 (47.9)	16 (43.2)
Rash	36 (50.7)	13 (35.1)
Rash maculo-papular	13 (18.3)	5 (13.5)
Vitiligo	8 (11.3)	2 (5.4)
Erythema	8 (11.3)	1 (2.7)

(continued)

Table 11: Common AEs (≥ 10% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-069 (24-month data cut-off) (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Nivolumab + ipilimumab** **N = 71**	**Ipilimumab** **N = 37**
Investigations	54 (76.1)	15 (40.5)
Aspartate aminotransferase increased	26 (36.6)	7 (18.9)
Alanine aminotransferase increased	24 (33.8)	6 (16.2)
Lipase increased	16 (22.5)	3 (8.1)
Blood alkaline phosphatase increased	11 (15.5)	4 (10.8)
Amylase increased	10 (14.1)	1 (2.7)
Weight decreased	9 (12.7)	1 (2.7)
Blood bilirubin increased	8 (11.3)	1 (2.7)
Respiratory, thoracic and mediastinal disorders	41 (57.7)	26 (70.3)
Cough	18 (25.4)	17 (45.9)
Dyspnoea	16 (22.5)	11 (29.7)
Oropharyngeal pain	5 (7.0)	5 (13.5)
Pneumonitis	8 (11.3)	2 (5.4)
Nasal congestion	5 (7.0)	4 (10.8)
Metabolism and nutrition disorders	43 (60.6)	19 (51.4)
Decreased appetite	16 (22.5)	12 (32.4)
Hyponatraemia	15 (21.1)	4 (10.8)
Dehydration	12 (16.9)	3 (8.1)
Hypoalbuminaemia	6 (8.5)	7 (18.9)
Hypokalaemia	7 (9.9)	5 (13.5)
Hyperglycaemia	5 (7.0)	4 (10.8)
Musculoskeletal and connective tissue disorders	39 (54.9)	21 (56.8)
Arthralgia	11 (15.5)	7 (18.9)
Myalgia	9 (12.7)	9 (24.3)
Back pain	11 (15.5)	4 (10.8)
Pain in extremity	9 (12.7)	5 (13.5)
Musculoskeletal pain	8 (11.3)	2 (5.4)
Nervous system disorders	35 (49.3)	19 (51.4)
Headache	20 (28.2)	7 (18.9)
Dizziness	10 (14.1)	5 (13.5)
Dysgeusia	9 (12.7)	1 (2.7)
Peripheral sensory neuropathy	3 (4.2)	4 (10.8)

(continued)

Table 11: Common AEs (≥ 10% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-069 (24-month data cut-off) (continued)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Nivolumab + ipilimumab N = 71**	**Ipilimumab N = 37**
Infections and infestations	30 (42.3)	14 (37.8)
Upper respiratory tract infection	4 (5.6)	4 (10.8)
Blood and lymphatic system disorders	21 (29.6)	13 (35.1)
Anaemia	17 (23.9)	11 (29.7)
Vascular disorders	23 (32.4)	11 (29.7)
Hypotension	8 (11.3)	5 (13.5)
Psychiatric disorders	24 (33.8)	9 (24.3)
Insomnia	16 (22.5)	6 (16.2)
Endocrine disorders	21 (29.6)	6 (16.2)
Hypothyroidism	13 (18.3)	5 (13.5)
Hypophysitis	9 (12.7)	3 (8.1)
Cardiac disorders	15 (21.1)	8 (21.6)
Eye disorders	20 (28.2)	2 (5.4)
Vision blurred	10 (14.1)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (8.5)	4 (10.8)

a: MedDRA version 18.1; SOC and PT designations taken from MedDRA without adaptation.
b: The events associated with progression were not excluded.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 12: Common SAEs (≥ 5% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-069 (24-month data cut-off)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Nivolumab + ipilimumab N = 71**	**Ipilimumab N = 37**
Study CA209-069 (data cut-off from 25 February 2016, 24 months)		
Overall rate of SAEs[b]	46 (64.8)	16 (43.2)
Gastrointestinal disorders	21 (29.6)	6 (16.2)
Colitis	11 (15.5)	2 (5.4)
Diarrhoea	6 (8.5)	3 (8.1)
Respiratory, thoracic and mediastinal disorders	8 (11.3)	3 (8.1)
Pneumonitis	5 (7.0)	0 (0)
General disorders and administration site conditions	6 (8.5)	4 (10.8)
Fever	5 (7.0)	2 (5.4)
Infections and infestations	8 (11.3)	2 (5.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (4.2)	4 (10.8)
Malignant neoplasm progression	2 (2.8)	2 (5.4)
Investigations	6 (8.5)	0 (0)
Metabolism and nutrition disorders	3 (4.2)	2 (5.4)
Vascular disorders	2 (2.8)	2 (5.4)
Hypotension	0 (0)	2 (5.4)
Nervous system disorders	1 (1.4)	2 (5.4)

a: MedDRA version 18.1; SOC and PT designations taken from MedDRA without adaptation.
b: The events associated with progression were not excluded.
BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 13: Common severe AEs with CTCAE grade 3–4 (≥ 5% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-069 (24-month data cut-off)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Nivolumab + ipilimumab N = 71**	**Ipilimumab N = 37**
Study CA209-069 (data cut-off from 25 February 2016, 24 months)		
Overall rate of AEs with CTCAE grade 3–4[b]	56 (78.9)	18 (48.6)
General disorders and administration site conditions	12 (16.9)	3 (8.1)
Fatigue	5 (7.0)	1 (2.7)
Gastrointestinal disorders	20 (28.2)	6 (16.2)
Diarrhoea	8 (11.3)	5 (13.5)
Colitis	10 (14.1)	1 (2.7)
Skin and subcutaneous tissue disorders	9 (12.7)	0 (0)
Rash	5 (7.0)	0 (0)
Investigations	23 (32.4)	6 (16.2)
Aspartate aminotransferase increased	9 (12.7)	0 (0)
Alanine aminotransferase increased	11 (15.5)	0 (0)
Lipase increased	9 (12.7)	1 (2.7)
Respiratory, thoracic and mediastinal disorders	7 (9.9)	4 (10.8)
Metabolism and nutrition disorders	11 (15.5)	5 (13.5)
Hyponatraemia	4 (5.6)	1 (2.7)
Dehydration	2 (2.8)	2 (5.4)
Nervous system disorders	5 (7.0)	2 (5.4)
Syncope	1 (1.4)	2 (5.4)
Infections and infestations	8 (11.3)	2 (5.4)
Blood and lymphatic system disorders	4 (5.6)	2 (5.4)
Vascular disorders	7 (9.9)	2 (5.4)
Hypotension	3 (4.2)	2 (5.4)
Endocrine disorders	2 (2.8)	2 (5.4)
Hypophysitis	1 (1.4)	2 (5.4)

a: MedDRA version 18.1; SOC and PT designations taken from MedDRA without adaptation.
b: The events associated with progression were not excluded.

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; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 14: Common discontinuations due to AEs (≥ 2% in at least one study arm), 30-day follow-up – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: nivolumab + ipilimumab vs. ipilimumab, study CA209-069 (24-month data cut-off)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Nivolumab + ipilimumab N = 71**	**Ipilimumab N = 37**
Study CA209-069 (data cut-off from 25 February 2016, 24 months)		
Overall rate of discontinuations due to AEs[b]	32 (45.1)	3 (8.1)
Gastrointestinal disorders	15 (21.1)	2 (5.4)
Colitis	10 (14.1)	0 (0)
Autoimmune colitis[c]	2 (2.8)	1 (2.7)
Diarrhoea	2 (2.8)	1 (2.7)
Investigations	5 (7.0)	0 (0)
Alanine aminotransferase increased	5 (7.0)	0 (0)
Aspartate aminotransferase increased	4 (5.6)	0 (0)
Endocrine disorders	3 (4.2)	1 (2.7)
Hypophysitis	1 (1.4)	1 (2.7)
Hypothyroidism	2 (2.8)	0 (0)
Nervous system disorders	3 (4.2)	0 (0)
Paresthesia	2 (2.8)	0 (0)
Respiratory, thoracic and mediastinal disorders	3 (4.2)	0 (0)
Pneumonitis	3 (4.2)	0 (0)

a: MedDRA version 18.1; SOC and PT designations taken from MedDRA without adaptation.
b: The events associated with progression were not excluded.
c: The designation is not a MedDRA term.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus