IQWiG Reports – Commission No. A17-21

Nivolumab (classical Hodgkin lymphoma) –

Addendum to Commission A16-76[1]

Addendum

Commission: A17-21
Version: 1.0
Status: 24 May 2017

[1] Translation of addendum A17-21 *Nivolumab (klassisches Hodgkin-Lymphom) – Addendum zum Auftrag A16-76* (Version 1.0; Status: 24 May 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Nivolumab (classical Hodgkin lymphoma) – Addendum to Commission A16-76

Commissioning agency:
Federal Joint Committee

Commission awarded on:
11 May 2017

Internal Commission No.:
A17-21

Address of publisher:
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]:

- Ulrike Seay
- Ulrich Grouven
- Thomas Kaiser

Keywords: nivolumab, Hodgkin disease, benefit assessment

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

Table of contents

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ASCT	autologous stem cell transplantation
BV	brentuximab vedotin
cHL	classical Hodgkin lymphoma
CSR	clinical study report
EMA	European Medicines Agency
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SCT	stem cell transplantation
SPC	Summary of Product Characteristics

1 Background

On 11 May 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-76 (Nivolumab – Benefit assessment according to §35a Social Code Book V [1]).

In Module 4 F of its dossier on nivolumab [2], the pharmaceutical company (hereinafter referred to as "the company") had presented a comparison of individual arms from different studies for the therapeutic indication of relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplantation (ASCT) and treatment with brentuximab vedotin (BV) for patients who are not candidates for further stem cell transplantation (SCT). This comparison included the single-arm nivolumab studies CA209-205 and CA209-039 and the retrospective analysis Cheah 2016 [3]. The comparison presented by the company was unsuitable for deriving conclusions on the added benefit of nivolumab in comparison with the appropriate comparator therapy specified by the G-BA for various reasons (see dossier assessment A16-76 [1]).

With its written comment on the dossier assessment [4] and after the oral hearing, the company presented, among other information, analyses on a new data cut-off of the nivolumab study CA209-205. Since, according to the company, the analyses were partly incorrect [5], it subsequently submitted a corrected version of these analyses following the oral hearing [6]. The G-BA commissioned IQWiG with the assessment of these analyses on the new data cut-off of the CA209-205 study.

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

In its original dossier, the company had not presented comparative studies, but an unadjusted comparison of individual study arms [2]. For nivolumab, it had included the single-arm studies CA209-039 and CA209-205. In compliance with the approval of nivolumab [7], the company had included patients with relapsed or refractory cHL after ASCT and BV treatment from these 2 studies. These were 152 patients in total: 15 of 23 patients of study CA209-039 and 80 patients of cohort B (total cohort B) and 57 (of 100) patients of cohort C of the CA209-205 study. The company had based its assessment mainly on a pooled analysis of these 152 patients. The company had used data on the data cut-off August 2015 for study CA209-039 and data on the data cut-off June 2016 for study CA209-205.

The company presented a new pooled analysis with its comment. For this analysis, it used a new data cut-off of the CA209-205 study (December 2016). Furthermore, it used patients who had received BV treatment *before* (and not after) ASCT in this analysis, however. This neither concurred with its approach in the dossier nor with the information provided in the Summary of Product Characteristics (SPC) and in the European Public Assessment Report (EPAR) by the European Medicines Agency (EMA) [8] on nivolumab nor with the approval of BV [9].

Both in the SPC on nivolumab and in the EPAR, the statements on efficacy are based on the "integrated efficacy population" consisting of the 15 patients in the CA209-039 study and of the 80 patients in cohort B of the CA209-205 study who were treated with BV *after* ASCT. In the EPAR, the results of the 57 patients in cohort C who also received BV *after* ASCT were additionally compared with the results of this "integrated efficacy population" [10].

In addition, it can be inferred from the SPC on BV that BV is only allowed to be administered *after* ASCT. Exceptions are only possible if ASCT (or a combination chemotherapy) is not an option for patients [9]. All patients now additionally analysed by the company received BV treatment *before* ASCT, however.

In summary, the 43 patients additionally included by the company did not concur with the target population of nivolumab and their treatment with BV before ASCT was not in compliance with the approval.

The company only presented the changed pooled analysis with the new data cut-off of the CA209-205 study, but no further study documents on the new data cut-off (e.g. updated clinical study report [CSR] of the CA209-205 study). No analyses on the original analysis population of patients with BV *after* ASCT were therefore possible. In addition, there was therefore no further information on individual outcomes (e.g. response rates on outcomes recorded with scales such as health-related quality of life). Irrespective of the question whether the company's data were suitable to prove the added benefit of nivolumab at all (see dossier assessment A16-76), the new analyses presented by the company were therefore overall not usable.

The pooled analyses subsequently submitted by the company are shown in Appendix A as presented by the company.

Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit from dossier assessment A16-76: The added benefit of nivolumab in comparison with the appropriate comparator therapy is not proven.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Nivolumab (klassisches Hodgkin-Lymphom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-76 [online]. 30.03.2017 [Accessed: 17.05.2017]. (IQWiG-Berichte; Volume 501). URL: https://www.iqwig.de/download/A16-76_Nivolumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Bristol-Myers Sqibb. Nivolumab (Opdivo): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 F; zur Behandlung des rezidivierenden oder refraktären klassischen Hodgkin-Lymphoms (cHL) bei Erwachsenen nach einer autologen Stammzelltransplantation (ASCT) und Behandlung mit Brentuximab Vedotin; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 16.12.2016 [Accessed: 17.05.2017]. URL: https://www.g-ba.de/downloads/92-975-1765/2016-12-16_Modul4F_Nivolumab.pdf.

3. Cheah CY, Chihara D, Horowitz S, Sevin A, Oki Y, Zhou S et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Ann Oncol 2016; 27(7): 1317-1323.

4. Bristol-Myers Squibb. Stellungnahme zum IQWiG-Bericht Nr. 501: Nicolumab (klassisches Hodgkin Lymphom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-76. 2017: [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/272/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

5. Gemeinsamer Bundesausschuss. Wirkstoff Nivolumab (nAWG): mündliche Anhörung gemäß 5. Kapitel § 19 Abs. 2 Verfahrensordnung des Gemeinsamen Bundesausschusses; stenografisches Wortprotokoll [online]. [Accessed: 23.05.2017]. URL: https://www.g-ba.de/downloads/91-1031-272/2017-05-09_Wortprotokoll_Nivolumab_nAWG_D-267.pdf.

6. Bristol-Myers Squibb. Zusatzdokument mit ergänzenden Auswertungen (Stand: 08.05.2017) als Anhang zur Stellungnahme zum IQWiG-Bericht Nr. 501: Nicolumab (klassisches Hodgkin Lymphom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-76. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/272/#tab/beschluesse/ in the document "Zusammenfassende Dokumentation"].

7. Bristol-Myers Squibb. Opdivo 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 11.2016 [Accessed: 23.11.2016]. URL: http://www.fachinfo.de.

8. European Medicines Agency. Opdivo: European public assessment report; summary for the public [online]. 12.01.2017 [Accessed: 17.05.2017].
URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003985/WC500189768.pdf.

9. Takeda. ADCETRIS 50 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. [Accessed: 10.10.2016]. URL: www.fachinfo.de.

10. European Medicines Agency. Opdivo: European public assessment report [online]. 13.10.2016 [Accessed: 22.05.2017].
URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003985/WC500219972.pdf.

Appendix A– Analyses presented by the company in the commenting procedure

Parameter	Nivolumab pooled (N=195)
N	195
Patients with event [n (%)]	27 (13.8)
Censored patients [n (%)]	168 (86.2)
Kaplan-Meier estimate [95% CI] (months)[(a)]	NC
CA209-205 (cohort B; N=80 and cohort C; N=100; data cut-off December 2016) and CA209-039 (N=15) (a) Kaplan-Meier estimate of the median time to event. 2-sided confidence intervals were calculated with the Brookmeyer and Crowley method (log-log transformation).	
NC: not calculable	

Figure 1: Mortality (studies CA209-205 and CA209-039) – table from analyses subsequently submitted by the company (analyses from 8 May 2017)

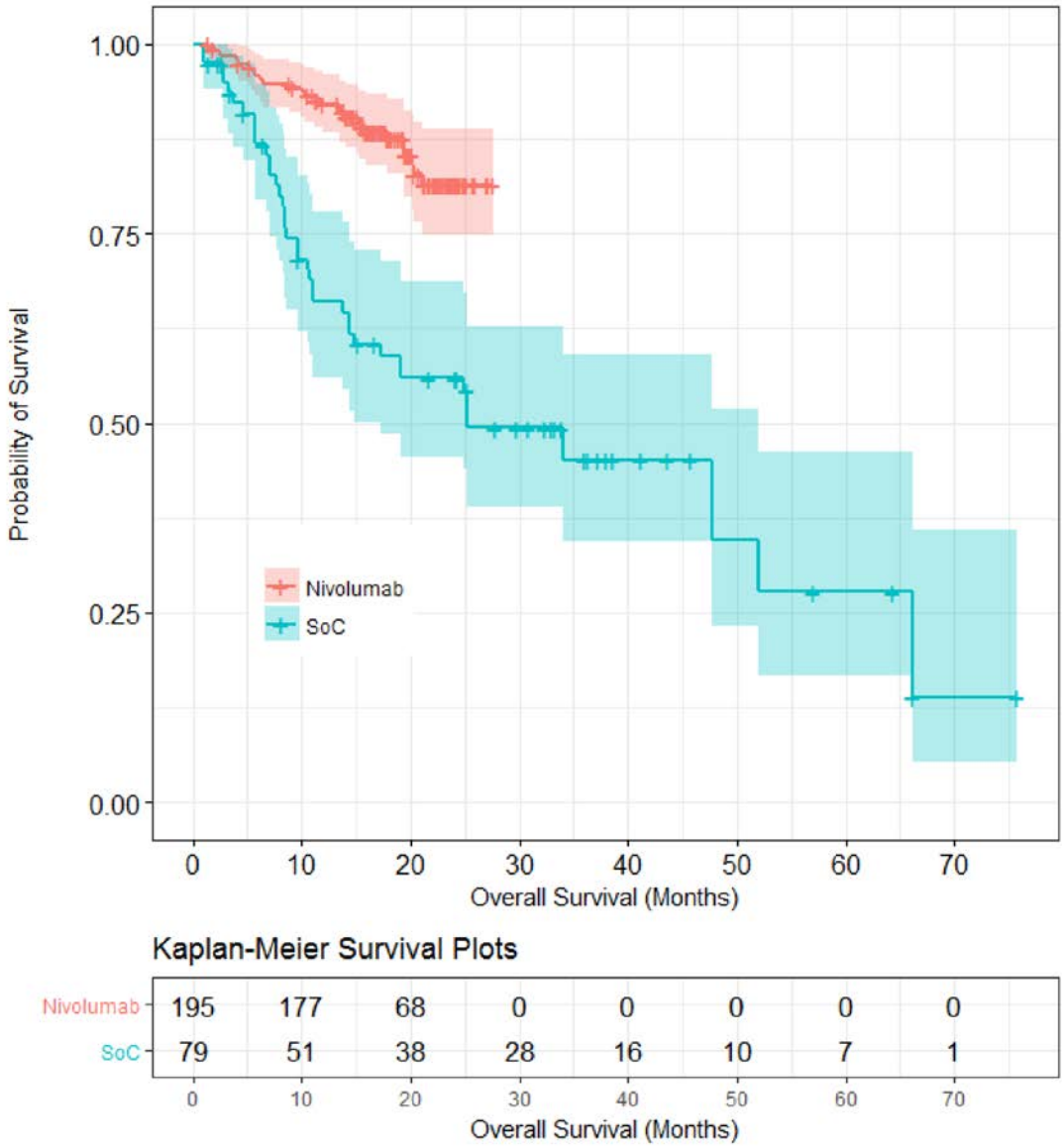

Figure 1: Kaplan-Meier curves of overall survival (OS): nivolumab – pooled from CA209-205 (cohort B; N=80 and cohort C; N=100; data cut-off December 2016) and patients in the therapeutic indication from CA209-039 (N=15) versus Cheah 2016 („SoC“, N=79 patients with documented subsequent therapy) (Cheah et al., 2016 [1])

Figure 2: Kaplan-Meier curves on overall survival from analyses subsequently submitted by the company (studies CA209-205 and CA209-039 and Cheah 2016) (analyses from 8 May 2017)[3]

[3] Figure and table headings introduced by bold font are the original headings provided by the company.

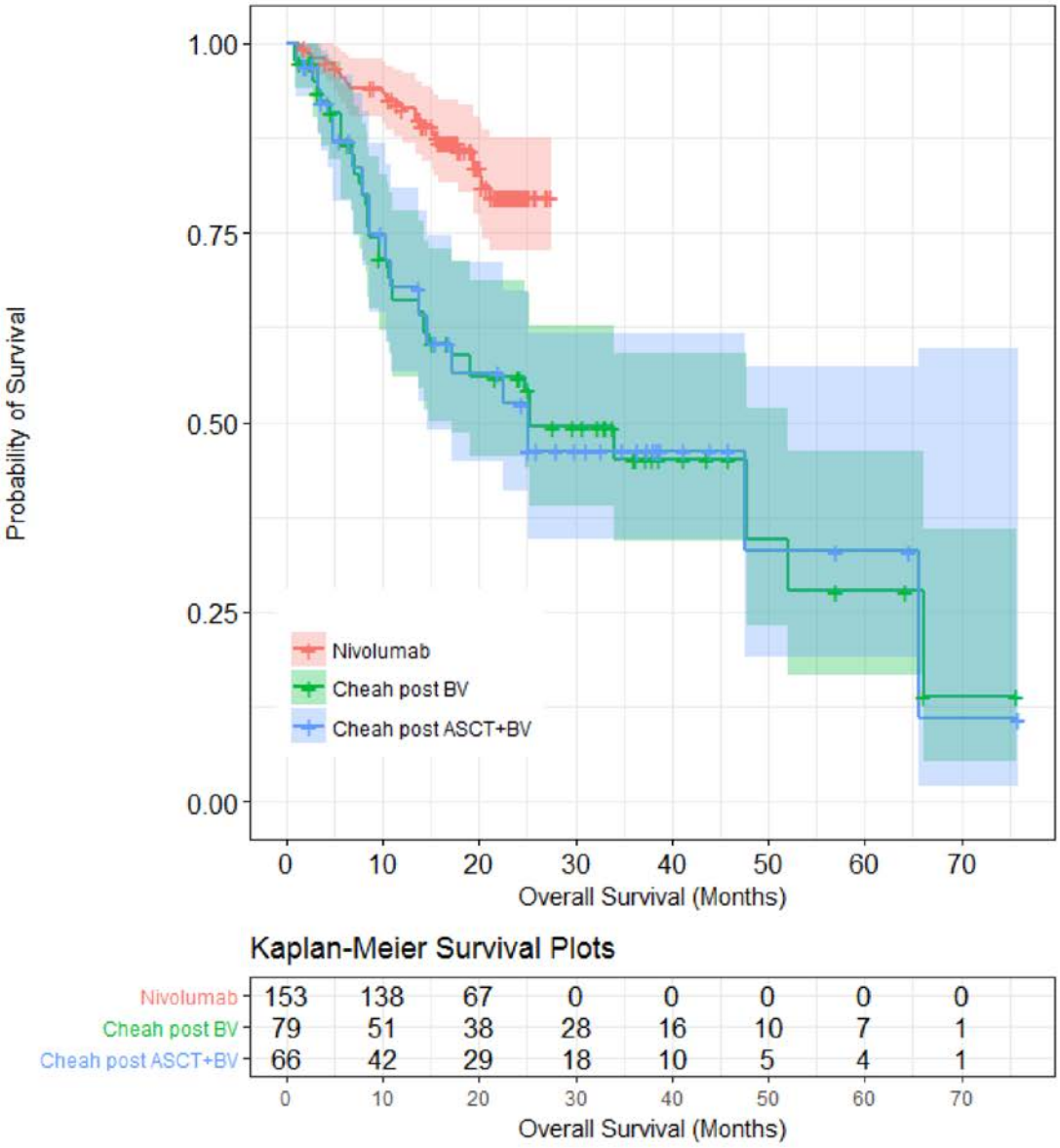

Figure 2: Sensitivity analysis: Kaplan-Meier curves of overall survival (OS): nivolumab – pooled from CA209-205 (cohort B; N=80 and cohort C treated like B; N=58; data cut-off December 2016) and patients in the therapeutic indication from CA209-039 (N=15) versus Cheah 2016 („Cheah post BV“, N=79 patients with documented subsequent therapy after brentuximab treatment and „Cheah post ASCT + BV“, N=66 patients with documented subsequent therapy after ASCT followed by brentuximab therapy) (Cheah et al., 2016 [1])

Figure 3: Sensitivity analysis of the Kaplan-Meier curves on overall survival from analyses subsequently submitted by the company (studies CA209-205 and CA209-039 and Cheah 2016) (analyses from 8 May 2017)

Table 4-10: Results for the outcome morbidity (health status according to EORTC QLQ-C30) – pooled from CA209-205 (cohort B and cohort C; data cut-off December 2016): clinically relevant deterioration

EORTC QLQ-C30 symptom scales	**N**	**Patients with clinically relevant deterioration n (%)**
Fatigue	161	59 (36.6%)
Nausea and vomiting	161	44 (27.3%)
Pain	161	61 (37.9%)
Dyspnoea	161	36 (22.4%)
Insomnia	161	55 (34.2%)
Impaired appetite	161	33 (20.5%)
Constipation	161	52 (32.3%)
Diarrhoea	161	60 (37.3%)
Financial difficulties	161	47 (29.2%)
CA209-205 (cohort B and cohort C; data cut-off December 2016) EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-Module		

Figure 4: Morbidity, symptoms – deterioration (EORTC QLQ-C30) (study CA209-205) – table from analyses subsequently submitted by the company (analyses from 8 May 2017)

Table 4-11: Results for the outcome morbidity (health status according to EORTC QLQ-C30) – pooled from CA209-205 (cohort B and cohort C; data cut-off December 2016): clinically relevant improvement

EORTC QLQ-C30 symptom scales	**N**	**Patients with clinically relevant improvement n (%)**
Fatigue	161	112 (69.9%)
Nausea and vomiting	161	30 (18.6%)
Pain	161	79 (49.1%)
Dyspnoea	161	59 (36.6%)
Insomnia	161	73 (45.3%)
Impaired appetite	161	63 (39.1%)
Constipation	161	33 (20.5%)
Diarrhoea	161	20 (12.4%)
Financial difficulties	161	67 (41.6%)
CA209-205 (cohort B and cohort C; data cut-off December 2016) EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-Module		

Figure 5: Morbidity, symptoms – improvement (EORTC QLQ-C30) (study CA209-205) – table from analyses subsequently submitted by the company (analyses from 8 May 2017)

Table 4-12: Results for the outcome health-related quality of life according to the EORTC QLQ-C30 – pooled from CA209-205 (cohort B and cohort C; data cut-off December 2016): clinically relevant deterioration

EORTC QLQ-C30 functional scales	**N**	**Patients with clinically relevant deterioration n (%)**
Physical functioning	161	36 (22.4%)
Role functioning	161	62 (38.5%)
Emotional functioning	161	50 (31.1%)
Cognitive functioning	161	77 (47.8%)
Social functioning	161	59 (36.6%)
Health status overall	161	50 (31.1%)
CA209-205 (cohort B and cohort C; data cut-off December 2016) EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-Module		

Figure 6: Health-related quality of life – deterioration (EORTC QLQ-C30) (study CA209-205) – table from analyses subsequently submitted by the company (analyses from 8 May 2017)

Table 4-13: Results for the outcome health-related quality of life according to the EORTC QLQ-C30 – pooled from CA209-205 (cohort B and cohort C; data cut-off December 2016): clinically relevant improvement

EORTC QLQ-C30 functional scales	**N**	**Patients with clinically relevant improvement n (%)**
Physical functioning	161	85 (52.8%)
Role functioning	161	86 (53.4%)
Emotional functioning	161	76 (47.2%)
Cognitive functioning	161	48 (29.8%)
Social functioning	161	89 (55.3%)
Health status overall	161	94 (58.4%)
CA209-205 (cohort B and cohort C; data cut-off December 2016) EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-Module		

Figure 7: Health-related quality of life – improvement (EORTC QLQ-C30) (study CA209-205) – table from analyses subsequently submitted by the company (analyses from 8 May 2017)

Table 4-14: Results for the outcome generic quality of life according to the EQ-5D – pooled from CA209-205 (cohort B and cohort C; data cut-off December 2016): clinically relevant deterioration

EQ-5D	**N**	**Patients with clinically relevant deterioration n (%)**
EQ-5D visual analogue scale score (EQ-5D VAS)	161	75 (46.6%)
EQ-5D visual analogue scale score (MID 10)	161	72 (44.7%)
EQ-5D utility score	161	60 (37.3%)
CA209-205 (cohort B and cohort C: data cut-of December 2016) EQ-5D = European Quality of Life Questionnaire 5 Dimensions		

Figure 8: Information on the EQ-5D VAS – deterioration (study CA209-205) – table from analyses subsequently submitted by the company (analyses from 8 May 2017)

Table 4-15: Results for the outcome generic quality of life according to the EQ-5D – pooled from CA209-205 (cohort B and cohort C; data cut-off December 2016): clinically relevant improvement

EQ-5D	**N**	**Patients with clinically relevant improvement n (%)**
EQ-5D visual analogue scale score (EQ-5D VAS)	161	111 (68.9%)
EQ-5D visual analogue scale score (MID 10)	161	103 (64.0%)
EQ-5D utility score	161	84 (52.2%)
CA209-205 (cohort B and cohort C: data cut-of December 2016) EQ-5D = European Quality of Life Questionnaire 5 Dimensions		

Figure 9: Information on the EQ-5D VAS – improvement (study CA209-205) – table from analyses subsequently submitted by the company (analyses from 8 May 2017)

Table 4-17: Results for the outcome tolerability: adverse events until 100 days after the end of treatment, analysis without recording of progression of the underlying disease – pooled from CA209-205 (cohort B; N=80 and cohort C; N=100; data cut-off December 2016) and CA209-039 (N =15)

AEs until 100 days after the end of treatment	**Nivolumab pooled (N=195)**
Any AE [n (%)]	193 (99.0)
Grade 3-4 AE [n (%)]	95 (48.7)
Serious AE [n (%)]	67 (34.4)
Treatment discontinuation due to AE[(a)] [n (%)]	19 (9.7)
CA209-205 (cohort B; N=80 and cohort C; N=100; data cut-off December 2016) and CA209-039 (N=15) (a) Values for adverse events until 30 days after the end of treatment.	
AE = adverse event	

Figure 10: Adverse events (studies CA209-205 and CA209-039) – table from analyses subsequently submitted by the company (analyses from 8 May 2017)

Table 4-9: Results for the outcome morbidity: B symptom resolution rate (population CA209-205 cohort B; N=80 and cohort C; N=100; data cut-off December 2016)

Parameter	**CA209-205 cohort B&C pooled (N=180)**
Number of patients with complete B symptom resolution	
Number of patients with B symptoms at baseline (N)	43
Number of patients with complete B symptom resolution [n (%)]	38 (88.4)
[95% CI][(a)]	[74.9; 96.1]
Duration until B symptom resolution (months)	
Mean	2.06
Median	1.87
Min./max.	0.9/5.6
Q1/Q3	1.87/2.07
SD	0.692
CA209-205 (cohort B; N=80 and cohort C; N=100; data cut-off December 2016), in study CA209-039, B symptoms were not recorded correspondingly. (a) Exact confidence interval according to Clopper-Pearson Q1: first quartile; Q3: third quartile; SD: Standard Deviation The duration until complete B symptom resolution was defined as difference between the time point of the first dose and the earliest time point without any B symptom (fever, night sweats and weight loss).	

Figure 11: B-symptoms (study CA209-205) – table from analyses subsequently submitted by the company (analyses from 8 May 2017)