IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A15-58

Nivolumab – Addendum to Commission A15-32[1]

Addendum

Commission: A15-58
Version: 1.0
Status: 13 January 2016

[1] Translation of addendum A15-58 *Nivolumab – Addendum zum Auftrag A15-32* (Version 1.0; Status: 13 January 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Nivolumab – Addendum to Commission A15-32

Commissioning agency:
Federal Joint Committee

Commission awarded on:
22 December 2015

Internal Commission No.:
A15-58

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]:

- Natalia Wolfram
- Thomas Kaiser
- Anke Schulz

Keywords: nivolumab, carcinoma – non-small-cell lung, benefit assessment

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

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 22 December 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-32 (Nivolumab – Benefit assessment according to §35a Social Code Book [SGB] V).

In its dossier [1], the pharmaceutical company (hereinafter referred to as "the company") presented results from the CA209-017 study to prove the added benefit for the patient population for which treatment with docetaxel is indicated. This study was used for the benefit assessment (research question 1 of dossier assessment A15-32 [2]). The results of this study on the outcomes regarding side effects presented by the company contained events caused by progression of the underlying disease. The survival time analyses for the outcome "serious adverse events (SAEs)" were not usable because of the large proportion of these events [2].

With its written comments, the company presented additional analyses on side effects (30-day follow-up) and an analysis on the outcome "all-cause mortality" at a later data cut-off (30 July 2015) [3]. After the oral hearing on nivolumab, the company submitted further analyses on side effects (100-day follow-up) on 30 December 2015 [4,5]. The G-BA commissioned IQWiG to analyse the new data presented by the company.

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 written comments and after the oral hearing, the company presented results of a new data cut-off on the outcome "overall survival" and further analyses on side effects based on adverse events for the CA209-017 study [3-5]. These data are assessed below. Finally, it is examined whether the data subsequently submitted change the conclusion of dossier assessment A15-32 on nivolumab.

2.1 Data on overall survival at the data cut-off 30 July 2015

Dossier assessment A15-32 was based on analyses of the CA209-017 study (nivolumab versus docetaxel) at the data cut-off on 15 December 2014. At this time point, no treatment switching had yet occurred in the CA209-017 study (treatment with nivolumab for patients in the docetaxel arm after disease progression). After this data cut-off on 15 December 2014, the study was ended prematurely and was continued as an extension study.

In its written comments, the company presented a new data cut-off from an open-label extension phase, which comprised the data on overall survival up to 30 July 2015. Overall, 6 patients had switched treatment from docetaxel to nivolumab up to this data cut-off. The data cut-off was not prespecified, but was conducted upon request of the regulatory authority European Medicines Agency (EMA) [6].

The data presented by the company were limited to analyses on overall survival in the total population; the company did not present subgroup analyses. The company also presented no data on morbidity, on health-related quality of life and on side effects for the new data cut-off.

In dossier assessment A15-32, a strong effect modification by the characteristic "age" (< 75 years, ≥ 75 years) was shown for the outcome "overall survival" based on the results of the data cut-off on 15 December 2014, which made a separate interpretation of the results necessary in these groups [2]. The company justified the fact that it did not conduct subgroup analyses regarding age by claiming that one patient (out of a total of 18 over 75 year olds) in the docetaxel arm had switched treatment to nivolumab. From the company's point of view, this can have a relevant influence on the result. The company's reasoning is not conclusive, however. The company's argument that the treatment switching of a single patient in the late phase of the study already has a relevant influence on the results of subgroup analyses would also apply to the results in the total population with 6 patients who switched treatment, i.e. the results in the total population at the data cut-off on 30 July 2015 would not be interpretable.

Since the effect modification for the subgroup characteristic "age" was strong in the first data cut-off (see dossier assessment A15-32), the second data cut-off was conducted with a time interval of about 6 months to the first data cut-off, and, in addition, the effect estimations of the 2 data cut-offs in the total population hardly differed, it can be assumed that there was an effect modification for the subgroup characteristic "age" also at the second data cut-off.

Hence a presentation of subgroup analyses for the second data cut-off would have been required for a complete assessment of the new results.

The analyses on overall survival in the total population (second data cut-off) subsequently submitted by the company therefore did not change the conclusions of dossier assessment A15-32. The data of the new data cut-off on 30 July 2015 for the total population are presented in Appendix A as additional information. Regarding the total population, these data confirm the result of the first data cut-off.

2.2 Analyses on adverse events

In its dossier, the company presented analyses on adverse events (AEs) on the basis of the 30-day follow-up after the end of treatment [1]. As described in dossier assessment A15-32, the analyses for the outcome "SAEs" were not usable because of the large proportion of events caused by progression of the disease.

In its written comments, the company presented new analyses on SAEs and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4), from which events that were probably caused by progression of the underlying disease were excluded. This analysis was based on a follow-up period of 30 days.

After the oral hearing, the company additionally presented results for the outcomes "SAEs", "severe AEs (CTCAE grade 3–4)" and "discontinuation due to AEs" on the basis of a follow-up period of 100 days after the end of treatment, in which the progression events were also not considered. For the outcome "discontinuation due to AEs" however, this analysis was less meaningful than the analysis 30 days after the end of treatment because it was impossible that treatment discontinuation occurred in the extended period.

The company presented no adequate analyses for the outcomes on specific AEs, which could only be interpreted in qualitative terms in the dossier assessment, for the 30-day follow-up or for the 100-day follow-up, although it was noted in dossier assessment A15-32 that these data were also lacking. In addition, the company presented no subgroup analyses on the new analyses on AEs.

Overall, the company presented no complete analysis for any of the 2 time points of follow-up. In the overall consideration of the original dossier and the data subsequently submitted, the data availability for the time point 30 days after the end of treatment was higher than for the later time point. However, only the data subsequently submitted on SAEs represented a meaningful supplementation in comparison with dossier assessment A15-32: The data on severe AEs were meaningfully interpretable also without cleansing for progression events, and subgroup analyses were missing for the cleansed analyses subsequently submitted. The company also presented no subgroup analyses for the cleansed analyses of SAEs. However, since no proof of an effect modification for different subgroup characteristics was shown in

the uncleansed data [1], it was assumed that the cleansed analysis could be interpreted on the basis of the total population of the study.

In the present addendum, only the cleansed analyses for the outcome "SAEs" based on the 30-day follow-up subsequently submitted were additionally considered. For the reasons described in dossier assessment A15-32, these analyses had a high risk of bias.

The cleansed data presented by the company for the 100-day follow-up are presented as additional information in Appendix B. The results showed no important deviation from the ones after 30 days of follow-up.

Results

Table 1 shows the analyses cleansed for progression events for the outcome "SAEs" on the CA209-017 study with nivolumab in comparison with docetaxel.

Table 1: Cleansed data on SAEs subsequently submitted, 30-day follow-up – RCT, direct comparison: nivolumab vs. docetaxel

Study Outcome category Outcome	Nivolumab		Docetaxel		Nivolumab vs. docetaxel	
	N	Median time to first AE in months [95% CI] Patients with event n (%)	N	Median time to first AE in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
CA209-017						
Side effects						
SAEs[c]	131	NC [7.26; NC] 45 (34.4)	129	2.60 [1.58; NC] 66 (51.2)	0.38 [0.25; 0.58]	< 0.001

a: Cox model, stratified by pretreatment with paclitaxel (yes, no) and region according to IVRS (USA/Canada, Europe, rest of the world).
b: Log-rank test, stratified by pretreatment with paclitaxel (yes, no) and region according to IVRS (USA/Canada, Europe, rest of the world).
c: Without events caused by progression of the underlying disease.
CI: confidence interval; HR: hazard ratio; IVRS: interactive voice response system; N: number of analysed patients; NC: not calculable or not achieved; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

There was a statistically significant difference in favour of nivolumab for the outcome "SAEs". This resulted in a hint of lesser harm from nivolumab in comparison with docetaxel. Due to the position of the confidence interval, the extent of added benefit was rated as "major" for this outcome [7].

2.3 Overall conclusion on added benefit

In comparison with dossier assessment A15-32, an additional positive effect of nivolumab for the outcome "SAEs" with the extent "major" resulted from the analyses subsequently submitted by the company.

The results included in the overall conclusion on the extent of added benefit are summarized in Table 2, taking into account dossier assessment A15-32 and the present addendum.

Table 2: Positive and negative effects from the assessment of nivolumab in comparison with docetaxel

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ Age < 75 years; indication of an added benefit – extent: "major" ≥ 75 years: lesser benefit/added benefit not proven Serious/severe side effects ▪ SAEs; hint of lesser harm – extent: "major" ▪ Treatment discontinuation due to AEs; hint of lesser harm – extent "major" ▪ Severe AEs (CTCAE grade 3–4): hint of lesser harm – extent: "major" ▪ Specific AEs (blood and lymphatic system disorders); indication of lesser harm – extent: "major" Non-serious/non-severe side effects ▪ Specific AEs (myalgia, peripheral neuropathy, alopecia); hint of lesser harm, extent: "considerable"	-
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event	

Patients < 75 years

In dossier assessment A15-32, there was an indication of major added benefit of nivolumab in comparison with docetaxel for patients < 75 years. The additional positive effect in the outcome "SAEs" (hint of lesser harm of nivolumab with the extent "major") did not change this conclusion, but supported it.

Patients ≥ 75 years

In dossier assessment A15-32, there was a hint of a non-quantifiable added benefit of nivolumab in comparison with docetaxel for patients ≥ 75 years. This was largely caused by the strong effect modification in the outcome "overall survival". The additional positive effect in the outcome "SAEs" (hint of lesser harm with the extent "major") did not change this conclusion, but supported it.

Summary

The data subsequently submitted by the company did not change the conclusions of the dossier assessment on nivolumab.

The result of the assessment of the added benefit of nivolumab in comparison with the ACT is summarized in Table 3.

Table 3: Nivolumab – extent and probability of added benefit

Research question	**Subindication**	**ACT**	**Subgroup**	**Extent and probability of added benefit**
1	Patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is indicated	Docetaxel	< 75 years	Indication of major added benefit
			≥ 75 years	Hint of a non-quantifiable added benefit
2	Patients with locally advanced or metastatic squamous NSCLC after pretreatment with chemotherapy for whom treatment with docetaxel is not indicated	BSC	Added benefit not proven	
ACT: appropriate comparator therapy; BSC: best supportive care; NSCLC: non-small cell lung cancer				

3 References

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6. European Medicines Agency. Nivolumab BMS: European public assessment report; product information [Deutsch] [online]. 27.07.2015 [accessed: 11.01.2016]. URL: http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/003840/WC500190648.pdf.

7. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden: Version 4.2. Köln: IQWiG; 2015. URL: https://www.iqwig.de/download/IQWiG_Methoden_Version_4-2.pdf.

Appendix A – Supplementary presentation of overall survival at the data cut-off on 30 July 2015 in the CA209-066 study (research question 1)

Table 4: Results (overall survival, data cut-off on 30 July 2015) – RCT, direct comparison: nivolumab vs. docetaxel

Study Outcome category Outcome	Nivolumab N	Nivolumab Median survival time in months [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median survival time in months [95% CI] Patients with event n (%)	Nivolumab vs. docetaxel HR [95% CI][a]	Nivolumab vs. docetaxel p-value[b]
CA209-017						
Mortality						
Overall survival	135	9.23 [7.33; 12.62][c] 103 (76.3)	137	6.01 [5.29; 7.39][c] 123 (89.8)	0.62 [0.47; 0.81][d]	< 0.001

a: Cox model, stratified by pretreatment with paclitaxel (yes, no) and region according to IVRS (USA/Canada, Europe, rest of the world).
b: Log-rank test, stratified by pretreatment with paclitaxel (yes, no) and region according to IVRS (USA/Canada, Europe, rest of the world).
c: The 2-sided 95% CI was calculated with a log-log transformation (according to Brookmeyer and Crowley).
d: Without censoring of the patients with treatment switching (total of 6 patients in the docetaxel arm).
CI: confidence interval; HR: hazard ratio; IVRS: interactive voice response system; N: number of analysed patients: RCT: randomized controlled trial; vs.: versus

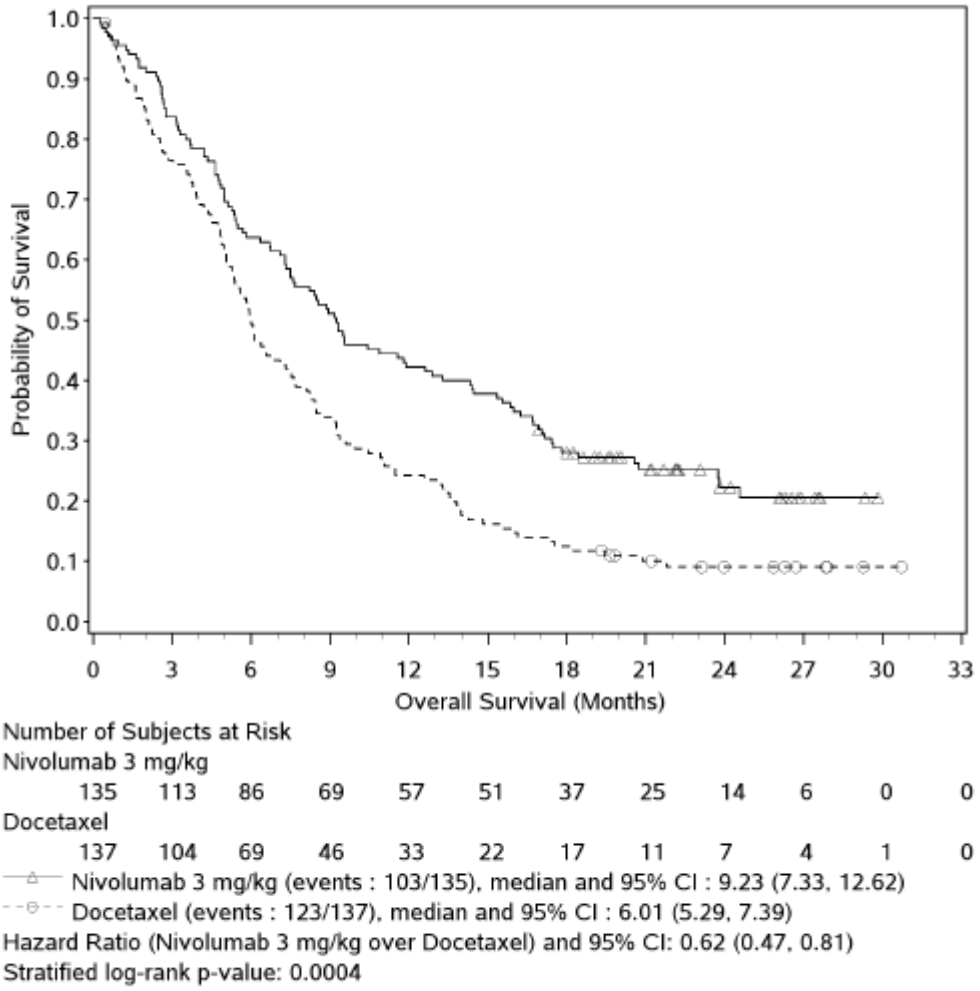

Figure 1: Kaplan-Meier curve for the outcome “overall survival” at the data cut-off 30 July 2015 (research question 1, nivolumab versus docetaxel)

Appendix B– Supplementary presentation of the results on side effects, 100-day follow-up, in the CA209-066 study (research question 1)

Table 5: Data on side effects cleansed for progression events subsequently submitted, 100-day follow-up – RCT, direct comparison: nivolumab vs. docetaxel

Study Outcome category Outcome	Nivolumab N	Nivolumab Median time to first AE in months [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median time to first AE in months [95% CI] Patients with event n (%)	Nivolumab vs. docetaxel HR [95% CI][a]	Nivolumab vs. docetaxel p-value[b]
CA209-017						
Side effects						
AEs[c] (supplementary information)	131	0.30 [0.26; 0.49] 124 (94.7)	129	0.16 [0.13; 0.23] 125 (96.9)	-	-
SAEs[c]	131	9.56 [7.10; NC] 58 (44.3)	129	2.56 [1.58; 3.98] 80 (62.0)	0.44 [0.31; 0.64]	< 0.001
Treatment discontinuation due to AEs[c]	131	NC [NC; NC] 12 (9.2)	129	NC [8.80; NC] 25 (19.4)	0.33 [0.16; 0.67]	0.002
Severe AEs (CTCAE grade 3–4)[c]	131	8.80 [4.17; NC] 65 (49.6)	129	0.33 [0.26; 1.18] 99 (76.7)	0.29 [0.20; 0.40]	< 0.001

a: Cox model, stratified by pretreatment with paclitaxel (yes, no) and region according to IVRS (USA/Canada, Europe, rest of the world).
b: Log-rank test, stratified by pretreatment with paclitaxel (yes, no) and region according to IVRS (USA/Canada, Europe, rest of the world).
c: Without events caused by progression of the underlying disease.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; IVRS: interactive voice response system; N: number of analysed patients; NC: not calculable or not achieved; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus