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# Nivolumab (non-squamous NSCLC) –

## Addendum to Commission A16-25[1]

# Addendum

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[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 |
| ASBI | average symptom burden index |
| $CI_u$ | upper limit of the confidence interval |
| EQ-5D | European Quality of Life-5 Dimensions |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| LCSS | Lung Cancer Symptom Scale |
| MID | minimally important difference |
| MMRM | mixed-effects model repeated measures |
| NSCLC | non-small cell lung cancer |
| PD-L1 | programmed cell death ligand 1 |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| TKI | tyrosine kinase inhibitor |
| VAS | visual analogue scale |

# 1 Background

On 5 September 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-25 (Nivolumab – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its written comments to the dossier assessment [2], the pharmaceutical company (hereinafter referred to as "the company") sent supplementary information, which went beyond the information provided in the dossier on nivolumab [3], to prove the added benefit. To be able to decide on the added benefit, the G-BA therefore requires further analyses.

The G-BA's commission referred to research question 1 of dossier assessment A16-25: patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy who are suitable for chemotherapy or treatment with a tyrosine kinase inhibitor (TKI). Specifically, the commission comprised the assessment of the analyses on symptoms and health status (data cut-off 18 March 2015) subsequently submitted and the assessment of the third data cut-off of study CA209-057 from 18 February 2016 subsequently submitted.

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, the company presented further analyses of the CA209-057 study [2,4]. These were further analyses on the outcomes "symptoms" and "health status" (data cut-off 18 March 2015) and analyses of the third data cut-off of the study from 18 February 2016 for the outcomes "overall survival" and "side effects".

The further analyses on symptoms and health status are assessed in Section 2.1, the data for the data cut-off 18 February 2016 subsequently submitted are assessed in Section 2.2. Section 2.3 contains the conclusions on the extent and probability of the added benefit of nivolumab under consideration of dossier assessment A16-25 and of the data assessed in the present addendum.

### 2.1 Further analyses on the outcomes "symptoms" and "health status" (data cut-off 18 March 2015)

The CA209-057 study recorded symptoms with the average symptom burden index (ASBI) of the Lung Cancer Symptom Scale (LCSS) and health status with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D). Both instruments are described in detail in dossier assessment A16-25 [1].

In its dossier, the company had presented no usable data for the outcomes recorded with these 2 instruments [1]:

- For the LCSS ASBI, the company's dossier contained analyses as time to deterioration (defined with a minimally important difference [MID] of 10 mm). These were not used for the benefit assessment because an MID of 15 mm, and not of 10 mm, is considered adequate for the ASBI [5]. The available mixed-effects model repeated measures (MMRM) analyses were not used because they were based on the data of fewer than 70% of the patients. With its comment, the company subsequently submitted analyses on the ASBI based on the validated MID of 15 mm. These were suitable for the benefit assessment.
- For health status, measured with the EQ-5D VAS, the company's dossier contained responder analyses as time to deterioration (defined with an MID of 7 mm). This MID represented the lower end of a range of 7 to 10 mm [6]. An additional sensitivity analysis based on the upper range (10 mm) of the MID is required for a valid interpretation of the results. This was not available in the company's dossier, however. The additionally available MMRM analyses were not used because they were based on the data of fewer than 70% of the patients. With its comment, the company subsequently submitted sensitivity analyses of the EQ-5D VAS based on the MID of 10 mm. These were suitable for the benefit assessment.

**Risk of bias**

Both for symptoms (LCSS ASBI) and for health status (EQ-5D VAS), a high proportion of patients (LCSS: 30%; EQ-5D VAS: 28%) was not considered in the analysis. Furthermore, the recording was not blinded. Due to the high proportion of censored patients, possible informative censoring can cause additional bias to the effect estimation. Overall, there was a high risk of bias for the outcomes on symptoms and health status.

**Results**

Table 1 shows the results of the outcomes on symptoms and health status.

Table 1: Results (morbidity) – RCT, direct comparison: nivolumab vs. docetaxel (data cut-off: 18 March 2015)

| Study<br>Outcome category | Nivolumab | | Docetaxel | | Nivolumab vs. docetaxel |
|---|---|---|---|---|---|
| Outcome | N | Median time to event (months) [95% CI]<br>Patients with event n (%) | N | Median time to event (months) [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[a] |
| **CA209-057** | | | | | |
| **Morbidity** | | | | | |
| Symptoms (LCSS ASBI)[b] | 292 | NA [12.5; NA]<br>77 (26.4) | 290 | 9.7 [5.8; NA]<br>83 (28.6) | 0.71 [0.52; 0.98]<br>0.034 |
| Health status (EQ-5D VAS[c]) | | | | | |
| MID 7 mm | 292 | 4.0 [2.7; 8.7]<br>121 (41.4) | 290 | 3.6 [2.4; 5.0]<br>127 (43.8) | 0.76 [0.59; 0.98]<br>0.032 |
| MID 10 mm | 292 | 5.1 [3.1; 11.2]<br>114 (39.0) | 290 | 4.3 [2.9; 5.9]<br>119 (41.0) | 0.75 [0.58; 0.97]<br>0.030 |

a: From Cox model.
b: Calculated as mean of the 6 LCSS symptom scales (loss of appetite, fatigue, cough, dyspnoea, haemoptysis, and pain). A (mean) increase in score by at least 15 points compared with baseline was considered as deterioration.
c: Information provided as time to deterioration.
ASBI: average symptom burden index; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MID: minimally important difference; n: number of patients with (at least one) event; LCSS: Lung Cancer Symptom Scale; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

***Morbidity***

*Symptoms (LCSS ASBI)*

There was a statistically significant result in favour of nivolumab for the outcome "symptoms" (LCSS ASBI). The difference was no more than marginal, however (upper limit of the confidence interval [$CI_u$] 0.98). Hence there was no hint of an added benefit of nivolumab in comparison with docetaxel; an added benefit is therefore not proven.

*Health status (EQ-5D VAS)*

For the outcome "health status" (EQ-5D VAS), there was a statistically significant result in favour of nivolumab both for the MID of 7 mm and for the MID of 10 mm. In each case, the difference was no more than marginal, ($CI_u$ 0.98 and 0.97).

In addition, there was an indication of an effect modification by the characteristic "programmed cell death ligand 1 (PD-L1) status" for this outcome (cut-off value 5%). Table 2 shows the corresponding results.

Table 2: Effect modifications (outcomes on morbidity – PD-L1 status) – RCT, direct comparison: nivolumab vs. docetaxel

| **Study** | **Nivolumab** | | **Docetaxel** | | **Nivolumab vs. docetaxel** | |
|---|---|---|---|---|---|---|
| **Outcome category**<br>**Characteristic**<br>**Outcome**<br>*Subgroup* | **N** | **Median time to event (months) [95% CI]**<br>**Patients with event n (%)** | **N** | **Median time to event (months) [95% CI]**<br>**Patients with event n (%)** | **HR [95% CI]** | **p-value** |
| **Study CA209-057** | | | | | | |
| **Morbidity** | | | | | | |
| **PD-L1 status (≥ 5%)[a]** | | | | | | |
| EQ-5D VAS MID 7 mm[b] | | | | | | |
| *Positive* | 95 | 8.7 [3.8; NA]<br>38 (40) | 86 | 7.0 [2.1; NA]<br>33 (38.4) | 0.51 [0.31; 0.83] | 0.006 |
| *Negative* | 136 | 2.4 [1.7; 9.6]<br>53 (39.0) | 138 | 3.3 [2.1; 4.9]<br>64 (46.4) | 0.92 [0.64; 1.33] | 0.668 |
| | | | | | Interaction: | 0.082 |
| EQ-5D VAS MID 10 mm[b] | | | | | | |
| *Positive* | 95 | 17.1 [4.9; NA]<br>35 (36.8) | 86 | 7.5 [2.8; NA]<br>30 (34.9) | 0.50 [0.30; 0.84] | 0.009 |
| *Negative* | 136 | 3.0 [2.0; 13.5]<br>50 (36.8) | 138 | 4.3 [2.4; 5.5]<br>60 (43.5) | 0.89 [0.61; 1.30] | 0.557 |
| | | | | | Interaction: | 0.119 |

a: Proportion of PD-L1-positive cells.

b: Information provided as time to deterioration.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MID: minimally important difference; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

A statistically significant result in favour of nivolumab was shown for PD-L1-positive patients. The upper limit of the confidence interval was below the marginality threshold of 0.9 both for the analysis with the MID of 7 mm and for the analysis with the MID of 10 mm. This resulted in a hint of an added benefit of nivolumab for PD-L1-positive patients. No statistically significant difference between the treatment groups was shown for PD-L1-

negative patients. Hence for PD-L1-negative patients, there was no hint of an added benefit of nivolumab in comparison with docetaxel; an added benefit is therefore not proven for these patients.

## 2.2 Analyses of the third data cut-off of the study from 18 February 2016

With the comment, the company presented analyses on the data cut-off from 18 February 2016 [2,4]. These were not contained in the original dossier.

The data presented by the company were incomplete with regard to content. On the one hand, the company presented no subgroup analyses for this data cut-off. In dossier assessment A16-25 [1], for example, there was proof of an effect modification by the characteristic "PD-L1 status" for each of the outcomes "overall survival" and "serious adverse events (SAEs)" at the data cut-off 18 March 2015. It remains unclear whether this also applied to the data cut-off 18 February 2016 or whether further relevant effect modifications were present at this data cut-off. On the other, the company presented no analyses on specific adverse events (AEs) at the data cut-off 18 February 2016.

In summary, the data subsequently submitted by the company for the data cut-off 18 February 2016 were incomplete and therefore not conclusively interpretable. They are presented as additional information in Appendix A.

## 2.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented in the following Table 3 for the outcomes "symptoms" and "health status" at outcome level. The methods used for this purpose are explained in the *General Methods* of IQWiG [7].

Table 3: Extent of added benefit at outcome level: nivolumab vs. docetaxel (analyses of the data cut-off 18 March 2015 subsequently submitted)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>*Subgroup* | **Nivolumab vs. docetaxel**<br>**Median time to event**<br>**Effect estimate [95% CI]; p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Morbidity** | | |
| Symptoms (LCSS ASBI), time to deterioration | Median: NA vs. 9.7 months<br>HR: 0.71 [0.52; 0.98]<br>p = 0.034<br>probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>lesser benefit/added benefit not proven[c] |
| Health status (EQ-5D VAS)[d], time to deterioration | Median: 4.0 vs. 3.6 months<br>HR: 0.76 [0.59; 0.98]<br>p = 0.032 | |
| PD-L1 (≥ 5%[e]) | | |
| *Positive* | 8.7 vs. 7.0 months<br>HR: 0.51 [0.31; 0.83]<br>p = 0.006<br>probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.8 \leq CI_u < 0.9$<br>added benefit, extent: "minor" |
| *Negative* | 2.4 vs. 3.3 months<br>HR: 0.92 [0.64; 1.33]<br>p = 0.668 | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>lesser benefit/added benefit not proven[c] |

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 $CI_u$.
c: Lesser benefit or added benefit is not proven because the effect size in the total population is only marginal.
d: Results provided for the lower threshold value (MID 7 points); direction of effect for upper threshold value (MID 10 points) consistent.
e: Proportion of PD-L1-positive cells.
ASBI: average symptom burden index; CI: confidence interval; $CI_u$: upper limit of CI; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MID: minimally important difference; LCSS: Lung Cancer Symptom Scale; PD-L1: programmed cell death ligand 1; VAS: visual analogue scale; vs.: versus

The following Table 4 shows the positive effects of nivolumab versus docetaxel under consideration of the results of dossier assessment A16-25 and of the present addendum. Changes resulting from the present addendum are presented in italics.

Table 4: Positive and negative effects from the assessment of nivolumab in comparison with docetaxel – research question 1 (patients who are suitable for chemotherapy or treatment with a TKI)

| **Positive effects** | **Negative effects** |
|---|---|
| Mortality<br>▪ Overall survival<br>▫ PD-L1 status (≥ 5%[a]) positive<br>indication of an added benefit – extent: "major" | – |
| *Non-serious symptoms/late complications*<br>▪ *Health status (EQ-5D VAS)*<br>▫ *PD-L1 status (≥ 5%)[a] positive*<br>*Hint of an added benefit - extent: "minor"* | |
| Serious/severe side effects<br>▪ SAEs<br>▫ PD-L1 status (≥ 5%)[a] positive<br>hint of lesser harm – extent: "considerable"<br>▪ Severe AEs (CTCAE grade 3–4): indication of lesser harm – extent: "major"<br>▪ Discontinuation due to AEs: hint of lesser harm – extent: "major"<br>▪ Blood and lymphatic system disorders (CTCAE grade 3–4): indication of lesser harm – extent: "major" | |
| Non-serious/non-severe side effects<br>▪ Alopecia: hint of lesser harm – extent: "considerable" | |
| *Italics:* changes resulting from the present addendum in comparison with dossier assessment A16-25.<br>a: Proportion of PD-L1-positive cells.<br>AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; PD-L1: programmed cell death ligand 1; SAE: serious adverse event; VAS: visual analogue scale | |

In comparison with dossier assessment A16-25, there is an additional positive effect with the extent "minor" for the outcome "health status" for patients with positive PD-L1 status. This did not change the conclusion of dossier assessment A16-25: In summary, there is an indication of a major added benefit of nivolumab for patients with locally advanced or metastatic non-squamous NSCLC after prior chemotherapy who are suitable for chemotherapy or treatment with a TKI.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

## 3 References

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## Appendix A – Supplementary presentation of the analyses subsequently submitted by the company on the data cut-off 18 February 2016

Table 5: Results (mortality, side effects) – RCT, direct comparison: nivolumab vs. docetaxel (data cut-off: 18 February 2016)

| Study<br>Outcome category<br>Outcome | Nivolumab<br>N | Nivolumab<br>Median time to event (months) [95% CI]<br>Patients with event n (%) | Docetaxel<br>N | Docetaxel<br>Median time to event (months) [95% CI]<br>Patients with event n (%) | Nivolumab vs. docetaxel<br>HR [95% CI]; p-value[a] |
|---|---|---|---|---|---|
| **CA209-057** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 292 | 12.2 [9.7; 15.1]<br>228 (78.1) | 290 | 9.5 [8.1; 10.7]<br>247 (85.2) | 0.75 [0.63; 0.91]<br>0.003 |
| **Side effects[b]** | | | | | |
| AEs | 287 | 0.3 [0.2; 0.3]<br>280 (97.6) | 268 | 0.1 [0.1; 0.1]<br>265 (98.9) | |
| SAEs | 287 | 12 [8.0; 19.0]<br>137 (47.7) | 268 | 6.5 [5.0; 9.0]<br>135 (50.4) | 0.84 [0.66; 1.07]<br>0.156 |
| Severe AEs (CTCAE grade 3-4) | 287 | 6.2 [3.8; 12.3]<br>161 (56.1) | 268 | 0.7 [0.4; 1.3]<br>201 (75.0) | 0.44 [0.36; 0.55]<br>< 0.001 |
| Discontinuation due to AEs | 287 | NA [NA; NA]<br>41 (14.3) | 268 | NA [10.6; NA]<br>55 (20.5) | 0.56 [0.37; 0.84]<br>0.005 |
| Alopecia | No data presented | | | | |
| Blood and lymphatic system disorders (CTCAE grade 3–4) | No data presented | | | | |

a: Log-rank test.
b: 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.

AE: adverse event; ASBI: average symptom burden index; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MID: minimally important difference; n: number of patients with (at least one) event; LCSS: Lung Cancer Symptom Scale; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

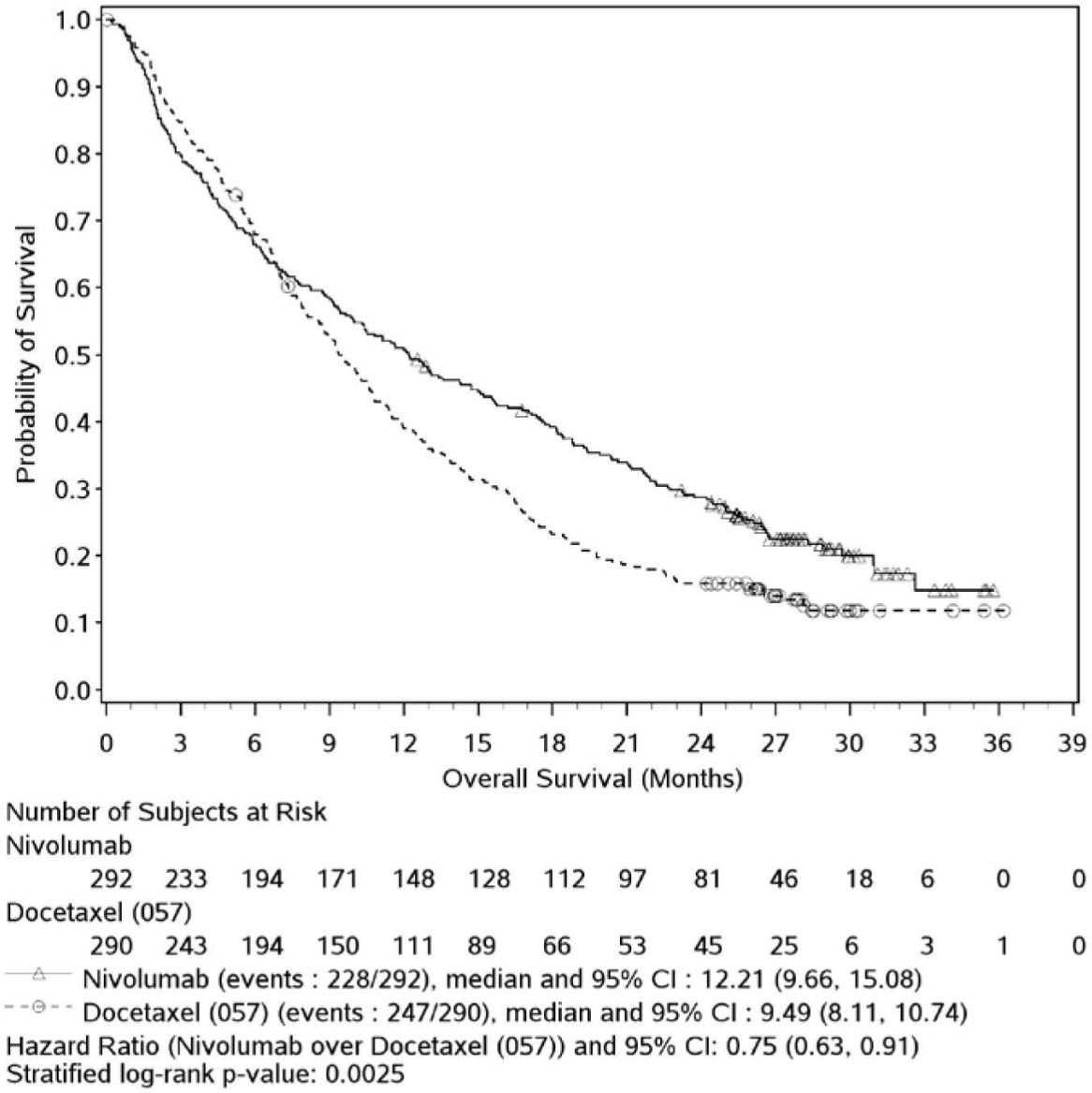


Figure 1: Kaplan-Meier curve for overall survival – RCT, direct comparison: nivolumab vs. docetaxel (data cut-off from 18 February 2016)