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Nivolumab (malignant pleural mesothelioma) –

Addendum to Commission A21-89[1]

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASBI	Average Symptom Burden Index
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
RCT	randomized controlled trial
VAS	visual analogue scale

1 Background

On 9 November 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A21-89 (Nivolumab – benefit assessment according to §35a Social Code Book V) [1].

To assess the benefit of nivolumab in combination with ipilimumab in comparison with the appropriate comparator therapy (ACT) in the treatment of untreated unresectable malignant pleural mesothelioma in adults with measurable disease, the randomized controlled trial (RCT) CA209-743 was included [1]. This study compared nivolumab + ipilimumab (hereinafter "intervention arm") with pemetrexed + cisplatin or pemetrexed + carboplatin (hereinafter "comparator arm"). In its dossier [2], the pharmaceutical company (hereinafter "company") submitted analyses on the Lung Cancer Symptom Scale – Mesothelioma Adaptation (LCSS-Meso) on symptoms and health-related quality of life. For LCSS-Meso, the planned observation durations differed between study arms. Both study arms had the same planned follow-up of 30 days and 120 days after the last dose of the study medication. However, patients in the comparator arm were followed up only until disease progression, while the study documents show that patients in the intervention arm were to be followed up beyond disease progression until study discontinuation. In dossier assessment A21-89 [1], this difference in planned survey periods was deemed inadequate. Regardless of the check of instrument validity, the data collected using LCSS-Meso were therefore unusable.

In its comments [3], the company clarified that LCSS-Meso in the intervention arm was surveyed only until the end of treatment, rather than until study discontinuation, plus at 2 follow-up visits after about 30 days and about 120 days.

The G-BA commissioned IQWiG with the following assessment of the additional analyses submitted by the company [3], taking into account the information provided in the dossier [2]:

- Reassessment of LCSS-Meso results (including check of instrument validity) based on the company's explanations in its comments regarding survey and follow-up durations
- Presentation of subpopulations (effect modification depending on histology) on European Quality of Life – 5 Dimensions (EQ-5D) visual analogue scale (VAS), provided such an effect modification existed

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

2 Assessment

2.1 Evaluation of LCSS-Meso results

According to the clarification provided in the company's comments [3], the LCSS-Meso survey was to follow up patients in the CA209-743 comparator arm until disease progression, but patients in the intervention arm until treatment end. For both study arms, follow-up observation was planned at 30 days and 120 days after the last dose of the study medication. In the comparator arm, follow-up was therefore independent of disease progression, provided that the study medication was completed as planned after 6 cycles or treatment was discontinued for reasons other than disease progression. A total of 62% of patients in the comparator arm completed treatment with the study medication as planned (see Table 1).

In both study arms, treatment continued until disease progression (as determined using Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1 and/or modified [m]RECIST criteria), unacceptable toxicity, treatment discontinuation, or reaching of the maximum treatment duration. In the intervention arm, it was possible to continue therapy beyond disease progression at the discretion of the investigator under certain conditions. As reported by the company in the oral hearing [4], this option was taken by only 5 patients in the intervention arm.

The information on patient flow provided in the company's dossier [2] show that in the intervention arm, treatment was discontinued, among other reasons, due to toxicity of the study medication (20%), adverse events (AEs) unrelated to the medication (4%), or achieving of maximum clinical benefit (3%) (see Table 1). A substantial majority of patients in the intervention arm (61%) discontinued treatment due to disease progression. For these patients, the LCSS-Meso survey was terminated based on the same criterion as used in the comparator arm, where patient follow-up was to continue until disease progression.

No data are available on the median or mean duration of actual LCSS-Meso follow-up in the CA209-743 study.

Table 1: Patient flow: treatment discontinuations – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a]

Study	Nivolumab + ipilimumab N = 300	Pemetrexed + platinum component[a] N = 284
CA209-743		
Treatment ongoing, n (%)	5 (1.7)	0 (0)
Treatment discontinuation, n (%)	295 (98.3)	284 (100)
Reasons:		
Disease progression	182 (60.7)	44 (15.5)
Toxicity of study medication	59 (19.7)	24 (8.5)
AE unrelated to the medication	12 (4.0)	9 (3.2)
Discontinuation by patient request	4 (1.3)	10 (3.5)
Consent withdrawn	6 (2.0)	3 (1.1)
Loss to follow-up	0 (0)	1 (0.4)
Maximum clinical benefit achieved	10 (3.3)	2 (0.7)
Poor/no cooperation	1 (0.3)	0 (0)
Patient no longer meeting participation criteria	4 (1.3)	0 (0)
Administrative reasons on the sponsor's side	2 (0.7)	0 (0)
Other reasons	11 (3.7)	2 (0.7)
Not reported	4[b] (1.3)	189[b] (66.5)

a. Cisplatin or carboplatin.
b. Among patients who discontinued treatment for the reason "not reported" on the electronic survey form, 3 patients in the intervention arm and 176 patients in the comparator arm had reached the maximum treatment duration (intervention arm: 2 years; comparator arm: 18 weeks).

AE: adverse event; n: number of patients in the category; N: number of patients who had received at least 1 dose of the study medication; RCT: randomized controlled trial

In summary, differences remain between treatment arms with regard to the planned patient follow-up. However, according to the clarification in the company's comments [3], the differences were not deemed grave enough to call into question the usability of the analyses. Overall, the planned follow-up durations for the CA209-743 intervention arm and comparator arm were deemed sufficiently comparable.

2.1.1 Validity check for LCSS-Meso

The company's dossier [2] presents results on symptoms and health-related quality of life, surveyed using the LCSS-Meso. The LCSS-Meso includes 8 items, which are each surveyed using a VAS (0 = best; 100 = poorest). Five of the items measure individual symptoms (loss of appetite, fatigue, cough, dyspnoea, and pain), with the Average Symptom Burden Index (ASBI) presenting the mean of these 5 items. The 3 items of symptom distress, interference with activity level, and global health-related quality of life relate to global aspects.

The company assigned the 3 items of symptom distress, interference with activity level, and global health-related quality of life to the category of health-related quality of life. However, these items are unsuitable for representing the complex construct of health-related quality of life. Therefore, the LCSS-Meso results on health-related quality of life as presented by the company were excluded from the benefit assessment.

In the dossier [2], the company submitted the items of loss of appetite, fatigue, cough, dyspnoea, and pain as well as ASBI for the outcome of symptoms in the outcome category of morbidity.

The LCSS-Meso ASBI represents symptoms in patients with malignant pleural mesothelioma and was used for the benefit assessment.

2.1.2 Operationalization of LCSS-Meso used for the benefit assessment

For the symptom outcome (LCSS-Meso ASBI), the company's dossier [2] presents responder analyses for time to definitive deterioration by 15 points and 10 points. In Module 4 N of its dossier [2], the company defines definitive deterioration as follows: deterioration by at least the response threshold without subsequent improvement to a value above the response threshold or deterioration by at least the response threshold and no subsequent values. The company's dossier [2] states that the definition likewise applies to all subsequent follow-up surveys. The company's analyses show that for some patients, an initial deterioration without further surveys was included in the analyses as an event; however, this was observed approximately equally in the two treatment arms and applied to few events (≤ 6%). Therefore, the results for time to definitive deterioration were used in the benefit assessment.

The LCSS-Meso ASBI response criterion of 15 points (scale range 0 to 100), which was used in the analyses presented by the company, fulfils the requirements for response criteria of reflecting with sufficient certainty a change that is perceivable for patients, as defined by the IQWiG General Methods [5]. The response criterion of 15 points for the LCSS-Meso ASBI, operationalized as time to permanent deterioration, is therefore used for the benefit assessment.

Only the aspects resulting from the assessment of the LCSS-Meso for the symptoms outcome are described below. The description of the results of the other outcomes included in the benefit assessment is found in dossier assessment A21-89 [1] or Section 2.2.

2.1.3 Risk of bias for the outcome of symptoms (LCSS-Meso)

For the results of the symptoms outcome (LCSS-Meso ASBI), the risk of bias is rated as high. Firstly, a high percentage (> 10%) of patients was excluded from the analysis because either no baseline value at study start or no further value over the course of the study was available for them. Secondly, for the patients included in the analysis, the return of questionnaires decreased over time and differed between treatment arms, potentially involving informative censoring. Lack of blinding with subjective outcome recording is an additional reason for the high risk of bias.

At most hints, e.g. of an added benefit, can therefore be pronounced for the outcome of symptoms.

2.1.4 Results for the outcome of symptoms (LCSS-Meso)

Table 2 shows the results on the outcome of symptoms, surveyed using LCSS-Meso. Appendix B shows the Kaplan-Meier curves on the time-to-event analysis of the LCSS-Meso ASBI with the response threshold of 15 points.

Table 2: Results on LCSS-Meso (morbidity) – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a]

Study Outcome category Outcome	Nivolumab + ipilimumab		Pemetrexed + platinum component[a]		Nivolumab + ipilimumab vs. pemetrexed + platinum component[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
CA209-743					
Morbidity					
Symptoms (LCSS-Meso ASBI[c])	303	NR [22.18; NC] 64 (21.1)	302	12.22 [8.02; NC] 59 (19.5)	0.58 [0.39; 0.86]; 0.006

a. Cisplatin or carboplatin.
b. Stratified Cox model and stratified logrank test; each stratified by sex and histology.
c: Calculated as the mean of the 5 LCSS-Meso symptom scales (appetite loss, fatigue, coughing, dyspnoea, and pain). Time to definitive deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).

ASBI: Average Symptom Burden Index; CI: confidence interval; HR: hazard ratio; LCSS-Meso: Lung Cancer Symptom Scale – Mesothelioma adaptation; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached ; RCT: randomized controlled trial

For the outcome of symptoms, measured using the LCSS-Meso, a statistically significant difference was found in favour of nivolumab + ipilimumab versus pemetrexed + platinum component. This results in a hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component.

2.1.5 Subgroups and other effect modifiers for the outcome of symptoms (LCSS-Meso)

For the present assessment, the following subgroup characteristics are relevant (see dossier assessment A21-89 [1]):

- sex (female versus male)
- age (< 65 years versus ≥ 65 to < 75 years versus ≥ 75 years)
- tumour histology (epithelioid vs. non-epithelioid)

- programmed death ligand-1 (PD-L1) status (positive vs. negative vs. not reported)

Overall, Kaplan-Meier curves on subgroup analyses are missing.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to be at least 10 events in at least 1 subgroup.

Only the results with an effect modification showing a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

In accordance with the methods described, no relevant effect modification was identified for the LCSS-Meso ASBI.

2.1.6 Determination of the outcome category for the outcomes on symptoms (LCSS-Meso)

For the following outcome, it cannot be inferred from the arguments in the company's dossier whether it is serious/severe or non-serious/non-severe. The classification for this outcome is justified.

The company classified the disease-related symptoms of loss of appetite (or subsequent weight loss), fatigue, coughing, and pain as serious because according to the guidelines [6-9], they represent characteristic symptoms of mesothelioma. It is unclear whether said symptoms are, per se, to be rated as serious/severe. No further information is available regarding a threshold for estimating the severity level. Therefore, the outcome of symptoms (LCSS-Meso ASBI) was assigned to the outcome category of non-serious/non-severe symptoms / late complications.

2.2 Assessment of subgroups and other effect modifications according to tumour histology on EQ-5D VAS

Dossier assessment A21-89 [1] used responder analyses for time to definitive deterioration by 15 points for health status, surveyed with EQ-5D VAS. The EQ-5D VAS response criterion of 15 points (scale range 0 to 100) fulfils the requirements for response criteria of reflecting with sufficient certainty a change that is perceivable for patients, as defined by the IQWiG General Methods [5]. The other responder analyses of EQ-5D VAS, using the response criteria of 7 points or 10 points, were presented as supplementary information in the dossier assessment's appendix [1].

For EQ-5D VAS, operationalized as time to definitive deterioration, subgroup analyses with associated interaction tests were available only for the response threshold of 7 points. The company's dossier [2] did not present subgroup analyses for the response threshold of 15 points used in the benefit assessment (see dossier assessment A21-89 [1]) nor for the response threshold of 10 points, which was presented as supplementary information. In general, the

dossier [2] lacked Kaplan-Meier curves on the subgroup analyses. The company did not, with its comments [3], subsequently submit any further results on EQ-5D VAS or Kaplan-Meier curves on subgroups.

Presented are only the results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup. The results are shown in Table 3.

Table 3: Subgroups on EQ-5D VAS – response threshold 7 points (morbidity) – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a]

Study **Outcome** **Characteristic** **Subgroup**	**Nivolumab + ipilimumab**		**Pemetrexed + platinum component[a]**		**Nivolumab + ipilimumab vs. pemetrexed + platinum component[a]**	
	N	**Median time to event in months [95 % CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95 % CI]** **Patients with event n (%)**	**HR [95 % CI][b]**	**p-value[b]**
CA209-743						
Health status (EQ-5D VAS)[c]						
Tumour histology						
Epithelioid	236	18.33 [15.47; 25.82] 91 (38.6)	235	13.73 [10.32; 18.33] 96 (40.9)	0.80 [0.60; 1.07]	0.134
Non-epithelioid	67	21,52 [9,69; NC] 24 (35.8)	67	8.02 [2.33; 10.97] 38 (56.7)	0.37 [0.22; 0.62]	< 0.001
Total					Interaction:	0.005[b]

a. Cisplatin or carboplatin.
b. Cox proportional hazards model with baseline value as well as treatment, subgroup attribute, and interaction term between treatment and subgroup attribute.
c. Time to definitive deterioration; defined as a score decrease of ≥ 7 points without improvement below the response threshold in any of the subsequent surveys.

CI: confidence interval; EQ-5D: European Quality of Life – 5 Dimensions; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; VAS: visual analogue scale

For EQ-5D VAS, operationalized as time to definitive deterioration by ≥ 7 points, an effect modification is found by the attribute of tumour histology. For patients with non-epithelioid tumour histology, a statistically significant difference was found in favour of nivolumab + ipilimumab versus pemetrexed + platinum component. For patients with epithelioid tumour histology, in contrast, there was no difference between treatment groups.

As discussed in dossier assessment A21-89 [1] and in Section 2.2 of the present addendum, responder analyses for time to definitive deterioration by ≥ 15 points were used for the benefit assessment. The effects in the total population are consistent for the different response thresholds (15 points, 10 points, and 7 points) (see Table 6 in Appendix A). As described above, not even in the commenting procedure did the company present any subgroup analyses for the response threshold of 15 points. Given the available evidence, however, it is assumed that, like for the response threshold of 7 points, there is an effect modification by the attribute of tumour histology and there is an advantage for nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with non-epithelioid tumour histology, but no difference for patients with epithelioid tumour histology. This results in a hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with non-epithelioid tumour histology. However, due to the missing subgroup analyses on the response threshold of 15 points, the extent of benefit is not quantifiable. For patients with epithelioid tumour histology, this results in no hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component; an added benefit is therefore not proven for these patients.

As in dossier assessment A21-89 [1], the outcome of health status (EQ-5D VAS) was assigned to the outcome category of non-serious/non-severe symptoms / late complications.

2.3 Probability and extent of added benefit

2.3.1 Overall conclusion on added benefit

Table 4 summarizes the results of dossier assessment A21-89 [1] and the present addendum, which were used for the overall conclusion on the extent of added benefit.

Table 4: Favourable and unfavourable effects from the assessment of nivolumab + ipilimumab in comparison with pemetrexed + platinum component[a]

Favourable effects	**Unfavourable effects**
Mortality ▪ Overall survival ▫ Non-epithelioid tumour histology indication of an added benefit – extent: major	–
Non-serious/non-severe symptoms/late complications ▪ **Symptoms: hint of an added benefit – extent: minor** ▪ **Health status:** ▫ **Non-epithelioid tumour histology** **hint of added benefit – extent: non-quantifiable**	–
Serious/severe side effects[b] ▪ Severe AEs ▫ Asthenia (severe AEs): hint of lesser harm – extent: considerable ▫ Anaemia (severe AEs): hint of lesser harm – extent: major ▫ Neutropoenia (severe AEs): hint of lesser harm – extent: major ▫ Thrombocytopoenia (severe AEs): hint of lesser harm – extent: considerable	Serious/severe side effects[b] ▪ SAEs - Epithelioid tumour histology Hint of greater harm – extent: major ▫ Immune-related SAEs: hint of greater harm – extent: major ▫ Renal and urinary disorders (SAEs) - Epithelioid tumour histology Hint of greater harm – extent: considerable ▫ Endocrine disorders (SAEs): hint of greater harm – extent: minor ▪ Severe AEs ▫ Immune-related severe AEs: hint of greater harm – extent major ▫ Lipase increased (severe AEs): hint of greater harm – extent: major ▫ Hepatobiliary disorders (severe AEs): hint of greater harm – extent: non-quantifiable ▫ Nervous system disorders (severe AEs): hint of greater harm – extent: minor ▫ Skin and subcutaneous tissue disorders (severe AEs): hint of greater harm – extent: minor ▫ Musculoskeletal and connective tissue disorders (severe AEs): hint of greater harm – extent: minor
Non-serious/non-severe side effects ▪ Nausea (AEs): hint of lesser harm – extent: considerable	Non-serious/non-severe side effects ▪ Diarrhoea (AEs): hint of greater harm – extent: considerable
Data on health-related quality of life were not recorded.	

a. Cisplatin or carboplatin.
b. When interpreting the results on side effects, it should be noted that the substantially shorter planned treatment duration and the associated discontinuation of follow-up in the comparator arm result in the hazard ratio reflecting only approximately the first 8 months after randomization.

Results printed in **bold** result from the data analysed in this addendum.
AEs: adverse events; SAE: serious adverse event

As described in dossier assessment A21-89 [1], the favourable effect in overall survival is found only in patients with non-epithelioid tumour histology. For this reason, favourable and unfavourable effects are weighed separately for patients with epithelioid versus non-epithelioid tumour histology.

For the outcome of symptoms, the LCSS-Meso results show another favourable effect of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for both patients with epithelioid tumour histology and those with non-epithelioid tumour histology.

For the outcome of health status, this results in a hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component, with the extent of non-quantifiable, for patients with non-epithelioid tumour histology.

No usable data are available for health-related quality of life (see Section 2.1 and dossier assessment A21-89 [1]).

The observed effects for the outcomes of symptoms and health status do not call into question the overall conclusion on added benefit drawn in dossier assessment A21-89 [1] for patients with non-epithelioid or epithelioid tumour histology.

All things considered, there is therefore no change in the overall conclusion on the added benefit of nivolumab + ipilimumab versus the ACT.

2.4 Summary

The data assessed in the present addendum on LCSS-Meso and EQ-5D VAS do not change the conclusion on the added benefit of nivolumab drawn in dossier assessment A21-89.

The following Table 5 shows the result of the benefit assessment of nivolumab, taking into account dossier assessment A21-89 and the present addendum.

Table 5: Nivolumab + ipilimumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of unresectable malignant pleural mesothelioma in adults	Treatment of physician's choice[b]	▪ Patients with epithelioid tumour histology[c]: added benefit not proven[d]. ▪ Patients with non-epithelioid tumour histology[c]: indication of considerable added benefit[d].

a. Presentation of the ACT specified by the G-BA.
b. Guidelines recommend the use of pemetrexed + cisplatin, pemetrexed + carboplatin or bevacizumab + cisplatin + pemetrexed. The drugs bevacizumab and carboplatin are not approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In a clinical trial, the combination therapies of pemetrexed + cisplatin, pemetrexed + carboplatin and bevacizumab + cisplatin + pemetrexed are deemed suitable comparators.
c. For which pemetrexed + cisplatin or pemetrexed + carboplatin represents the appropriate therapy upon the physician's discretion.
d. Except for 1 patient, only patients with an ECOG-PS of 0 or 1 were included in the CA209-743 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

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Appendix A – Overview of EQ-5D VAS results for the response thresholds of 7, 10, and 15 points

Table 6: Overview of the results on EQ-5D VAS (morbidity) – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a]

Study Outcome category Outcome	Nivolumab + ipilimumab		Pemetrexed + platinum component[a]		Nivolumab + ipilimumab vs. pemetrexed + platinum component[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
CA209-743					
Morbidity					
Health status (EQ-5D VAS[c])					
7 points	303	18.89 [16.33; 25.82] 115 (38.0)	302	12.68 [9.95; 15.01] 134 (44.4)	0.67 [0.52; 0.86]; 0.002
10 points	303	20.14 [18.04; 26.09] 107 (35.3)	302	12.85 [10.32; 15.70] 130 (43.0)	0.63 [0.49; 0.82]; < 0.001
15 points[d]	303	26,15 [22,64; NC] 81 (26.7)	302	16.69 [15.01; 21.75] 99 (32.8)	0.65 [0.49; 0.88]; 0.005

a. Cisplatin or carboplatin.
b. Cox model, adjusted by baseline value.
c. Time to definitive deterioration; defined as a score decrease by the response threshold without improvement below the response threshold in any of the subsequent surveys.
d. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100) and used for the benefit assessment.

CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life – 5 Dimensions; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; VAS: visual analogue scale

Appendix B – Kaplan-Meier curves on LCSS-Meso ASBI

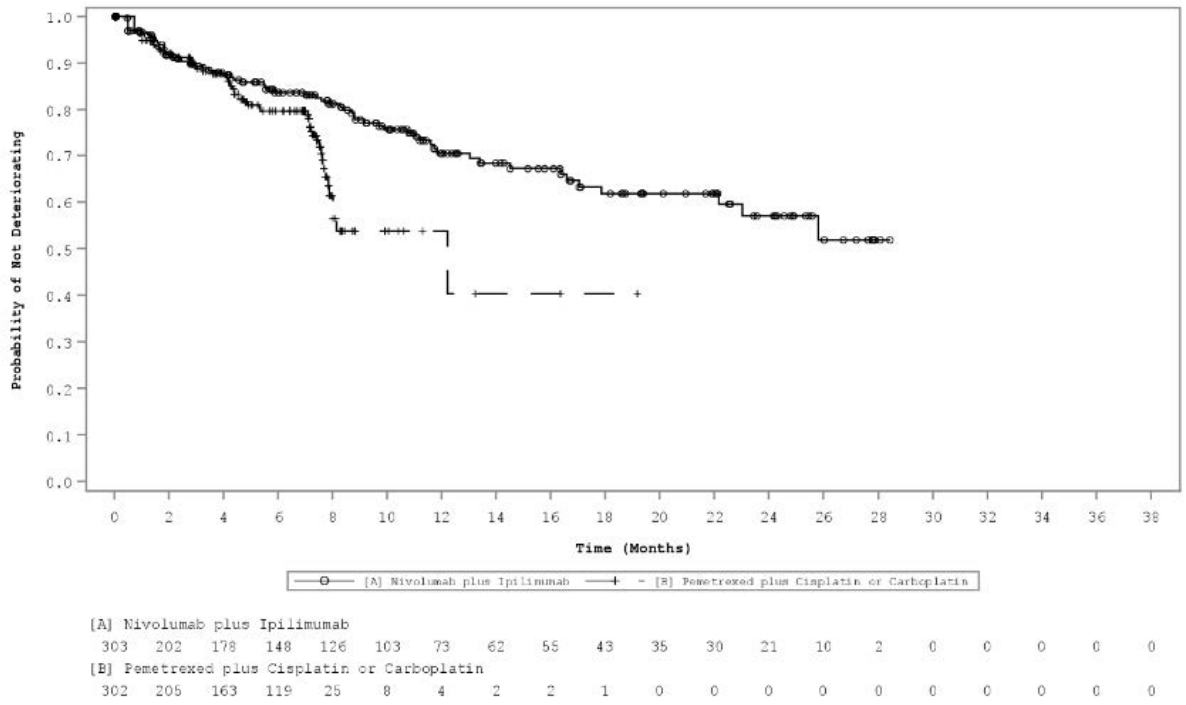

Figure 1: Kaplan-Meier curves for the outcome of symptoms (LCSS-Meso ASBI; time to definitive deterioration, response criterion of 15 points) from the study