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Nivolumab (NSCLC) –

Addendum to Commission A20-118[1]

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
ASBI	average symptom burden index
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
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
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PT	Preferred Term
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 29 April 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-118 (Nivolumab – Benefit assessment according to §35a Social Code Book V) [1].

Dossier assessment A20-118 used the CA209-9LA study, which included adult patients with metastatic non-small cell lung cancer (NSCLC) without sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation who had not received prior systemic therapy. The study compared nivolumab + ipilimumab + platinum-based chemotherapy (hereinafter referred to as "intervention arm") with platinum-based chemotherapy (hereinafter referred to as "comparator arm"). For the benefit assessment, only the subpopulation of patients with programmed cell death ligand 1 (PD-L1) expression < 50% and non-squamous histology was used for research question 2 because an adequate implementation of the Pharmaceutical Directive on the off-label use of carboplatin [2] was assumed only for this subpopulation.

The G-BA commissioned IQWiG with the assessment of the following additional data submitted by the pharmaceutical company (hereinafter referred to as the "company") [3,4] under consideration of the information provided in the dossier [5]:

- Use of the subpopulation of patients with squamous NSCLC with PD-L1 expression < 50%
- Analysis of the total population (squamous and non-squamous) for all patient-relevant outcomes, taking into account the information and analyses provided in the dossier and in the written comments of the company, provided that no effect modification regarding histology is shown.

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

Research question 2 (PD-L1 expression < 50%)

Study CA209-9LA [3,6-9] is used for answering research question 2 (first-line treatment in adult patients with metastatic NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression < 50%). Hereinafter, the subpopulation of patients with metastatic non-squamous or squamous NSCLC whose tumours have a PD-L1 expression < 50% (n = 497) is described and analysed.

2.1 Study and patient characteristics

In the following, only those aspects are described that (in contrast to the dossier assessment) result from the summarized consideration of the subpopulation of patients with squamous and non-squamous histology. The description of the study characteristics of the CA209-9LA study can be found in dossier assessment A20-118 [10]. Table 1 presents the intervention characteristics for the patients with squamous histology together with the intervention characteristics of the patients with non-squamous histology already known from the dossier assessment.

Table 1: Characteristics of the intervention – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Study	Intervention	Comparison
CA209-9LA	Nivolumab 360 mg IV every 3 weeks, for a maximum of 24 months + ipilimumab 1 mg/kg BW IV every 6 weeks, for a maximum of 24 months + histology-based chemotherapy for a maximum of 2 cycles of 3 weeks each ▪ squamous histology: carboplatin AUC 6 IV + paclitaxel 200 mg/m² BSA IV on day 1 of each cycle ▪ non-squamous histology[b]: cisplatin 75 mg/m² BSA IV + pemetrexed 500 mg/m² BSA IV on day 1 of each cycle *or* carboplatin AUC 5–6 IV + pemetrexed 500 mg/m² BSA IV on day 1 of each cycle ▪ If nivolumab was discontinued, the therapy with ipilimumab also had to be stopped. If ipilimumab was discontinued, nivolumab could be continued. ▪ If ipilimumab or nivolumab was discontinued, therapy with chemotherapy[a] could be continued until 2 cycles were reached.	Histology-based chemotherapy for a maximum of 4 cycles of 3 weeks each: ▪ squamous histology: carboplatin AUC 6 IV + paclitaxel 200 mg/m² BSA IV on day 1 of each cycle ▪ non-squamous histology[b]: cisplatin 75 mg/m² BSA IV + pemetrexed 500 mg/m² BSA IV on day 1 of each cycle *or* carboplatin AUC 5–6 IV + pemetrexed 500 mg/m² BSA IV on day 1 of each cycle ▪ Patients with non-squamous histology and no disease progression could continue to receive maintenance therapy with pemetrexed 500 mg/m² BSA IV on day 1 of each cycle from cycle 5 onwards at the discretion of the investigator.
	▪ Interval prolongations of the dose due to toxicity were possible. Dose adjustments were only allowed for chemotherapy[a]. ▪ Premedication for the administration of chemotherapy[a] was carried out in accordance with the SPC or local standards.	

Table 1: Characteristics of the intervention – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Study	Intervention	Comparison
	Non-permitted pretreatment ▪ systemic antineoplastic therapy as primary therapy for stage III or IV NSCLC ▪ systemic immunosuppressive therapies within 14 days before start of the study medication (with the exception of systemic glucocorticoids < 10 mg/day prednisone equivalent) **Permitted pretreatment** ▪ chemotherapy (adjuvant and neoadjuvant) and radiotherapy in early stage or locally advanced stage NSCLC up to ≥ 6 months before enrolment ▪ palliative radiotherapy of non-CNS metastases CNS up to ≥ 14 days before start of the study medication ▪ treatment of CNS metastases: either completion of glucocorticoid therapy or stable or reduced dose to ≤ 10 mg/day prednisone or equivalent ≥ 2 weeks before start of the study medication ▪ major surgery ≥ 14 days before start of the study medication **Concomitant treatment** ▪ inhaled, topical, ocular, intraarticular, and intranasal glucocorticoids ▪ adrenal replacement glucocorticoids > 10 mg prednisone equivalent ▪ < 3 weeks glucocorticoids for prophylaxis of allergic reactions or for treatment of non-autoimmune conditions ▪ bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events from bone metastases if therapy was initiated before start of the study medication ▪ palliative radiotherapy[c] and surgical resection of symptomatic bone, skin or CNS lesions ▪ palliative treatment of lesions causing haemoptysis	

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. The choice of cisplatin or carboplatin was made by the investigator before randomization.
c. Ipilimumab and nivolumab had to be interrupted 1 week before, during and after radiotherapy.

AUC: area under the curve; BSA: body surface area; BW: body weight; CNS: central nervous system; IV: intravenous; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RANK-L: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial

A total of 719 patients were included in the CA209-9LA study. For the present research question 2, only the subpopulation of patients with PD-L1 expression < 50% is relevant (n = 497, intervention arm n = 262; comparator arm n = 235). The type of chemotherapy was dependent on the histology of the tumour: patients with squamous histology received carboplatin in combination with paclitaxel; patients with non-squamous histology received either cisplatin or carboplatin, each in combination with pemetrexed. The platinum component was chosen by the investigator before randomization on the basis of eligibility criteria not described in more detail by the company.

The use of the study medication (see Table 1) in both study arms complies with the requirements of the respective Summaries of Product Characteristics (SPCs) or guidelines [11-

16]. Only the 200 mg/m^2 dose of paclitaxel specified in the study protocol for patients with squamous histology deviates slightly from the requirements of the SPC, which specifies 175 mg/m^2 in combination with cisplatin [17]. The SPCs do not contain any further information on the combination of paclitaxel or pemetrexed with carboplatin. In the comparator arm, up to 4 cycles of chemotherapy were administered; then patients with non-squamous histology and no disease progression could receive maintenance therapy with pemetrexed from cycle 5. However, the number of patients who received maintenance therapy with pemetrexed cannot be inferred from Module 4 K. Patients with squamous histology did not receive maintenance therapy in the comparator arm after cycle 4.

Data cut-offs

A total of 2 data cut-offs are available for the CA209-9LA study (see dossier assessment A20-118). In accordance with the company, the second data cut-off is used for the present assessment.

Treatment duration and follow-up observation

The information on the planned duration of follow-up observation can be found in dossier assessment A20-118.

Characteristics of the study population

The patient characteristics of the subpopulation with PD-L1 expression < 50% are presented in Table 2.

Table 2: Characteristics of the study population – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Study Characteristic Category	Nivolumab + ipilimumab + platinum-based chemotherapy[a] N[b] = 262	Platinum-based chemotherapy[a] N[b] = 235
CA209-9LA		
Age [years], mean (SD)	64 (8)	63 (10)
Sex [F/M], %	27/73	29/71
Family origin, n (%)		
White	234 (89)	203 (86)
African American	3 (1)	4 (2)
Asian	23 (9)	22 (9)
Other	2 (1)	6 (3)
Region, n (%)		
Europe	159 (61)	136 (58)
North America	21 (8)	22 (9)
Rest of the world	61 (23)	55 (23)
Asia	21 (8)	22 (9)
ECOG PS, n (%)[c]		
0	89 (34)	77 (33)
1	172 (66)	158 (67)
Tumour histology, n (%)		
Squamous cell carcinoma	81 (31)	75 (32)
Non-squamous cell carcinoma	181 (69)	160 (68)
Smoking status, n (%)		
Active/former	229 (87)	205 (87)
Never	33 (13)	30 (13)
Disease stage[d], n (%)		
Stage IV	243 (93)	222 (94)
Recurrent to metastatic disease	19 (7)	13 (6)
Metastases at baseline[e]		
Brain metastases, n (%)	45 (17)	35 (15)
Liver metastases, n (%)	45 (17)	57 (24)
Bone metastases, n (%)	72 (27)	71 (30)
PD-L1 status, n (%)		
< 1%	135 (52)	129 (55)
≥ 1%	127 (48)	106 (45)

Table 2: Characteristics of the study population – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Study Characteristic Category	Nivolumab + ipilimumab + platinum-based chemotherapy[a] N[b] = 262	Platinum-based chemotherapy[a] N[b] = 235
Treatment of physician's choice[f], n (%)		
Carboplatin + paclitaxel	80 (31)	73 (31)
Carboplatin + pemetrexed	123 (47)	103 (44)
Cisplatin + pemetrexed	57 (22)	49 (21)
Not reported	2 (1)	8 (3)
Treatment discontinuation, n (%)[g]	209 (80)	149 (66)
Study discontinuation, n (%)[h]	42 (16)	33 (15)

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. No ECOG PS was reported for one patient in the intervention arm.
d. Staging according to IASCLC and UICC.
e. There is no further information on metastatic sites.
f. According to the company, in the comparator arm, one patient was treated with carboplatin, cisplatin and pemetrexed and one patient with carboplatin, paclitaxel and pemetrexed.
g. Referring to all patients who received at least one dose of the study medication (intervention arm N = 260; comparator arm N = 227). The most common reasons for treatment discontinuation in both treatment arms were progression (intervention arm 48.1%; comparator arm 47.6%) and toxicity of the study medication (intervention arm 20.8%; comparator arm 7.9%).
h. Referring to all patients who received at least one dose of the study medication (intervention arm N = 260; comparator arm N = 227). According to the company, the most common reason for study discontinuation in both treatment arms was death (intervention arm 15.0%; comparator arm 12.8%). It is unclear why these data differ from the event rates for the outcome "overall survival".

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IASCLC: International Association for the Study of Lung Cancer; M: male; n: number of patients in the category; N: number of randomized (or included) patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; UICC: Union for International Cancer Control

Patient characteristics were largely balanced between the 2 study arms. The mean age of the patients was 64 and 63 years, the majority were male and > 80% were of white family origin. 66 and 67% of the patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1. The tumour histology of about 1 third of the patients was classified as squamous cell carcinoma. The vast majority of patients were active or former smokers.

Information on the course of the study

Table 3 presents information on the treatment and observation durations for individual outcomes for the subpopulation for research question 2.

Table 3: Information on the course of the study – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%)

Study **Duration of the study phase** **Outcome category**	**Nivolumab + ipilimumab + platinum-based chemotherapy[a]** **N = 260[b]**	**Platinum-based chemotherapy[a]** **N = 227[b]**
CA209-9LA		
Treatment duration [months]		
Median [min; max]	5.63 [0.0; 23.5]	2.37 [0.0; 22.8]
Mean (SD)	7.60 (ND)	4.43 (ND)
Observation period [months]		
Overall survival		
Median [min; max]	14.09 [0.2; 27.2]	10.22 [0.1; 26.7]
Mean (SD)	12.99 (6.65)	10.94 (6.49)
Morbidity		
Symptoms (LCSS ASBI)	ND	
Health status (EQ-5D VAS)	ND	
Health-related quality of life	Outcome not recorded	
Side effects	ND	

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. All patients who received at least one dose of the study medication.

ASBI: average symptom burden index; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; max.: maximum; min: minimum; N: number of analysed patients; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The median treatment duration was more than twice as long in the intervention arm as in the comparator arm. This is mainly due to the fact that, in the intervention arm, continued treatment with nivolumab + ipilimumab was possible until disease progression, unacceptable intolerances, or reaching the maximum treatment duration. In the comparator arm, in contrast, all patients with squamous histology were treated with a maximum of 4 cycles of chemotherapy and only some of the patients with non-squamous histology received maintenance therapy with pemetrexed after the initial 4 cycles.

The median observation period between the 2 treatment arms is comparable for the outcome "overall survival"; no data on the observation period are available for the remaining outcomes. The follow-up observation for adverse events (AEs) was only up to 100 days, and for the Lung Cancer Symptom Scale (LCSS) up to 115 days after the last dose of study medication (see dossier assessment). The differences in treatment duration due to the differences in treatment structure between the intervention arm and the comparator arm described above resulted in very different observation periods between the individual patients for the outcome "LCSS" and the side effect outcomes. However, differences in the observation periods exist not only between

the intervention arm and the comparator arm, but also within the comparator arm depending on the histology, as the pemetrexed maintenance therapy was only possible for patients with non-squamous histology. See below for the effects on the outcome-specific risk of bias.

Subsequent therapies

The information on subsequent therapies can be found in dossier assessment A20-118. The subsequent therapies administered are presented in Appendix B.

Risk of bias across outcomes (study level)

Analogous to dossier assessment A20-118, the risk of bias across outcomes was rated as low for the CA209-9LA study.

2.2 Results

Outcomes included

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded with the LCSS average symptom burden index (ASBI)
  - health status recorded with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS)
- Side effects
  - serious adverse events (SAEs)
  - severe AEs (operationalized as Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3 events)
  - discontinuation due to AEs (discontinuation of at least one drug component)
  - immune-related AEs (SAEs and severe AEs)
  - further specific AEs, if any

Table 4 shows for which outcomes data for the subpopulation with PD-L1 expression < 50% were available in the study included.

Table 4: Matrix of outcomes – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%)

Study	Outcomes									
	Overall survival	Symptoms (LCSS ASBI)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs	Immune-related severe AEs[b]	Further specific AEs[b, c]
CA209-9LA	Yes	Yes	Yes	No[d]	Yes	Yes	Yes[e]	Yes[f]	Yes[f]	Yes

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events are considered (MedDRA coding): anaemia (PT, severe AEs), lipase increased (PT, severe AEs), amylase increased (PT, severe AEs), hepatobiliary disorders (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), endocrine disorders (SOC, severe AEs).
d. Outcome not recorded.
e. Operationalized as discontinuation of at least one drug component.
f. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome "adverse events of specific interest" ("select AEs") is used.

AE: adverse event; ASBI: average symptom burden index; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; MedDRA: Medical Dictionary for Regulatory Activities; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

- The uncertainties and ambiguities described in dossier assessment A20-118 regarding the operationalization of time to definitive deterioration for the outcomes "LCSS ASBI" and "EQ-5D VAS" were sufficiently explained by the company in its comments. The company clarified that the definition applied permanently to all further follow-up recordings, which were not allowed to show an improvement below the response threshold. Its analyses submitted with the comments show that, although for some patients a first deterioration without further recordings was included as an event in the analyses, this was largely balanced between the treatment arms and affected only a few events (LCSS ASBI approx. 10%, EQ-5D VAS < 5%) [3]. Irrespective of this, the analyses subsequently submitted for the time to first deterioration confirmed the results of the analyses for the time to definitive deterioration of the LCSS ASBI and the EQ-5D VAS. Accordingly, the results for the time to definitive deterioration were used for the benefit assessment.

  The response criteria of 15 points each for the LCSS ASBI (scale range of 100 points) and the EQ-5D VAS (scale range of 100 points) used in the analyses submitted or

subsequently submitted by the company correspond to the criteria described in the *General Methods* of the Institute for response criteria that represent a noticeable change for patients with sufficient certainty [18]. The other responder analyses presented by the company on the EQ-5D VAS with a response criterion of 7 and 10 points are presented as supplementary information in Appendix D, as this response criterion was used in previous assessments in the therapeutic indication of NSCLC.

- As described in dossier assessment A20-118, the operationalization of discontinuation of all drug components due to AEs in the CA209-9LA study, which was used by the company, cannot be interpreted in a meaningful way. For the subpopulation with PD-L1 expression < 50%, information on discontinuation of at least one drug component due to AEs was available in the dossier. In deviation from the company, this operationalization is therefore used for the benefit assessment.
- Dossier assessment A20-118 used no analyses of immune-related AEs, as the suitability of the AEs of specific interest presented by the company could not be reliably assessed as an operationalization for immune-related AEs. In its comments, the company clarified that the outcome of AEs of specific interest, which it referred to as "select AEs", comprised all events that belonged to the typical immune-related AEs and for which treatment of the AEs with immunosuppression (e.g. with corticosteroids) could, but did not have to, be necessary. In addition, it presented the list of Preferred Terms (PTs) that were included as events in the analysis of the "select AEs". This operationalization is considered a sufficient approximation for immune-related AEs. Both severe AEs (CTCAE grade ≥ 3) and SAEs were considered. Analyses based on System Organ Classes (SOCs) or PTs are not available for the subpopulation with PD-L1 expression < 50% for the immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3).

Risk of bias

Table 5 describes the risk of bias for the results of the relevant outcomes.

Table 5: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nivolumab + ipilimumab + chemotherapy[a] vs. chemotherapy[a] (research question 2: PD-L1 expression < 50%)

Study	Study level	Outcomes									
		Overall survival	Symptoms (LCSS ASBI)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Immune-related SAEs[d]	Immune-related severe AEs[b, d]	Further specific AEs[b, e]
CA209-9LA	L	L	H[f, g]	H[f]	–[h]	H[g]	H[g]	H[f]	H[g]	H[g]	H[g]

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as discontinuation of at least one drug component.
d. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome "adverse events of specific interest" ("select AEs") is used.
e. The following events are considered (MedDRA coding): anaemia (PT, severe AEs), lipase increased (PT, severe AEs), amylase increased (PT, severe AEs), hepatobiliary disorders (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), endocrine disorders (SOC, severe AEs).
f. Lack of blinding in subjective recording of outcomes.
g. Different observation periods between the treatment arms; potentially informative censorings (especially in patients with squamous histology).
h. Outcome not recorded.

AE: adverse event; ASBI: average symptom burden index; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; LCSS: Lung Cancer Symptom Scale; MedDRA: Medical Dictionary for Regulatory Activities; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias for the results of the outcome "overall survival" was rated as low. This concurs with the company's assessment.

Due to the open-label study design with subjective recording of outcomes, the risk of bias for the results of the outcomes "LCSS ASBI", "EQ-5D VAS" and "discontinuation due to AEs" was rated as high. For the results of the outcome "LCSS ASBI", there were additional potentially informative censorings, leading to a high risk of bias (see next paragraph). The latter does not apply to the results of the EQ-5D VAS, as this outcome, like overall survival, was followed up until death (see dossier assessment).

The risk of bias of the results of the following outcomes was rated as high: LCSS ASBI, SAEs, severe AEs (CTCAE grade ≥ 3), immune-related SAEs, immune-related severe AEs (CTCAE grade ≥ 3), and other specific AEs. The outcomes on LCSS ASBI and on side effects were only recorded for the period of treatment with the study medication plus 115 and 100 days,

respectively. Whereas the study medication in the intervention arm (i.e. maintenance therapy with nivolumab + ipilimumab) could be given until disease progression, treatment with the study medication in the comparator arm was only for 4 cycles (3 weeks each), with the exception of the optional pemetrexed maintenance therapy for non-squamous histology. For all outcomes mentioned, this resulted in marked differences in the observation periods of the individual patients with potentially informative censorings.

However, due to the optional pemetrexed maintenance therapy of patients with non-squamous histology, not all patients in the comparator arm were censored after 4 cycles plus planned follow-up observation, but only those with squamous histology as well as those with non-squamous histology without pemetrexed maintenance therapy. As a result, in the comparator arm, only patients with non-squamous histology and pemetrexed maintenance therapy were still at risk after approx. 6 months and were included in the effect estimation using hazard ratio. Such a comparison is not appropriate. Therefore, in the present situation, it is examined on an outcome-specific basis whether the event time analyses can be used for the assessment.

Results

Table 6 summarizes the results of the comparison of nivolumab + ipilimumab + platinum-based chemotherapy versus platinum-based chemotherapy alone in patients with metastatic NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression < 50%. Where necessary, data from the company's dossier are supplemented by Institute's calculations.

Event time analyses for the outcome "EQ-5D VAS" with the response criteria of 7 and 10 points are presented in Appendix D. Kaplan-Meier curves on the event time analyses are presented in Appendix A. Tables on common AEs, SAEs and severe AEs (CTCAE ≥ 3) are presented in Appendix C. Data on discontinuation due to AEs based on SOCs or PTs are not available for the subpopulation with PD-L1 expression < 50% for discontinuation of at least one drug component.

Table 6: Results (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Study **Outcome category** **Outcome**	**Nivolumab + ipilimumab + platinum-based chemotherapy[a]**		**Platinum-based chemotherapy[a]**		**Nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[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**
CA209-9LA					
Mortality					
Overall survival	262	16.16 [13.77; 20.53] 137 (52.3)	235	10.25 [8.67; 12.22] 167 (71.1)	0.61 [0.49; 0.77]; < 0.001[b]
Morbidity					
Symptoms (LCSS ASBI[c])	262	NA 43 (16.4)	235	NA [16.33; NC] 29 (12.3)	0.78 [0.47; 1.29] 0.330[d]
Health status (EQ-5D VAS[e])	262	22.21 [20.14; NC] 65 (24.8)	235	17.81 [16.53; NC] 57 (24.3)	0.75 [0.52; 1.09] 0.127[d]
Health-related quality of life	No outcomes recorded in this category				
Side effects					
AEs (supplementary information)[f]	260	0.13 [0.13; 0.23] 259 (99.6)	227	0.20 [0.13; 0.30]; 222 (97.8)	–
SAEs[f]	260	5.09 [3.55; 7.26] 169 (65.0)	227	11.17 [6.80; NC] 98 (43.2)	1.52 [1.18; 1.95]; 0.001[b]
Severe AEs[f, g]	260	2.83 [1.94; 3.45] 201 (77.3)	227	3.71 [2.76; 5.59] 87 (38.3)	1.27 [1.02; 1.58]; 0.031[b]
Discontinuation due to AEs[f, h]	260	NA 82 (31.5)	227	NA 32 (14.1)	1.98 [1.31; 2.99]; < 0.001[b]
Immune-related AEs (supplementary information)	*260*	*1.64 [1.02; 2.17]; 202 (77.7)*	*227*	*8.34 [5.26; 11.10]; 108 (47.6)*	–
Immune-related SAEs	260	NA 57 (21.9)	227	NA 14 (6.2)	3.27 [1.82; 5.88]; < 0.001[b]
Immune-related severe AEs[g]	260	NA 75 (28.8)	227	NA 21 (9.3)	2.94 [1.81; 4.79]; < 0.001[b]
Specific AEs					
Anaemia (PT, severe AEs[g])	260	NA 22 (8.5)	227	NA 39 (17.2)	0.46 [0.27; 0.78]; 0.003[b]

Table 6: Results (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Study **Outcome category** **Outcome**	**Nivolumab + ipilimumab + platinum-based chemotherapy[a]**		**Platinum-based chemotherapy[a]**		**Nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[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**
Lipase increased (PT, severe AEs[g])	260	NA 21 (8.1)	227	NA 3 (1.3)	4.75 [1.40; 16.05]; 0.006[b]
Amylase increased (PT, severe AEs[g])	260	NA 10 (3.8)	227	NA 0 (0)	NC[i]; 0.006[b]
Hepatobiliary disorders (SOC, severe AEs[g])	260	NA 18 (6.9)	227	NA 0 (0)	NC[i]; 0.001[b]
Skin and subcutaneous tissue disorders (SOC, severe AEs[g])	260	NA 17 (6.5)	227	NA 3 (1.3)	4.80 [1.40; 16.40]; 0.006[b]
Endocrine disorders (SOC, severe AEs[g])	260	NA 11 (4.2)	227	NA	NC[i]; 0.006[b]

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. Effect and CI: presumably unstratified Cox proportional hazards model, log-log transformation (according to Brookmeyer and Crowley); p-value: presumably unstratified log-rank test.
c. Time to definitive deterioration; defined as an increase in score of ≥ 15 points without improvement below the response threshold in any of the subsequent recordings.
d. Effect and CI: presumably unstratified Cox proportional hazards model, log-log transformation (according to Brookmeyer and Crowley) with baseline values as covariates; p-value: presumably unstratified log-rank test.
e. Time to definitive deterioration; defined as a decrease in score of ≥ 15 points without improvement below the response threshold in any of the subsequent recordings.
f. Without recording of progression of the underlying disease.
g. Operationalized as CTCAE grade ≥ 3.
h. Operationalized as discontinuation of at least one drug component.
i. Since no events occurred in one study arm, the HR cannot be estimated.

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; LCSS: Lung Cancer Symptom Scale; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available data, at most indications, e.g. of an added benefit, can be derived for the outcome “overall survival”, and at most hints for all other outcomes due to the high risk of bias.

Mortality

Overall survival

For the outcome "overall survival", there was a statistically significant difference in favour of nivolumab + ipilimumab + platinum-based chemotherapy. In addition, there was an effect modification by the characteristic "brain metastases at baseline" for the outcome. There was a statistically significant difference in favour of nivolumab + ipilimumab + platinum-based chemotherapy for both patients with brain metastases at baseline and patients without brain metastases at baseline. For both subgroups, this resulted in an indication of an added benefit of nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy, but with different extents (see Section 2.2.1).

Morbidity

Symptoms (LCSS ASBI)

No statistically significant difference between the treatment groups was shown for the outcome "LCSS ASBI" (response threshold of 15 points). This resulted in no hint of an added benefit of nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between the treatment groups was shown for the outcome "EQ-5D VAS" (response threshold of 15 points). This resulted in no hint of an added benefit of nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

Health-related quality of life

The CA209-9LA study did not record health-related quality of life. This resulted in no hint of an added benefit of nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs (discontinuation of at least one drug component)

A statistically significant difference to the disadvantage of nivolumab + ipilimumab + platinum-based chemotherapy was shown for each of the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs" (discontinuation of at least one drug component). In each case, this resulted in a hint of greater harm from nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy.

Specific AEs

Immune-related SAEs and severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of nivolumab + ipilimumab + platinum-based chemotherapy was shown for the outcomes "immune-related SAEs" and "immune-related severe AEs (CTCAE grade ≥ 3)". In each case, there was a hint of greater harm from nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy.

Anaemia (PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of nivolumab + ipilimumab + platinum-based chemotherapy was shown for the outcome "anaemia" (severe AEs [CTCAE grade ≥ 3])". In addition, there was an effect modification by the characteristic "tumour histology" in this outcome. For patients with non-squamous histology, there was a hint of lesser harm from nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy. For patients with squamous histology, however, there was no hint of lesser or greater harm of nivolumab + ipilimumab + platinum-based chemotherapy.

Lipase increased (PT, severe AEs [CTCAE grade ≥ 3]), amylase increased (PT, severe AEs [CTCAE grade ≥ 3]), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]), endocrine disorders (SOC, severe AEs [CTCAE grade ≥ 3])

There was a statistically significant difference to the disadvantage of nivolumab + ipilimumab + platinum-based chemotherapy for each of the following outcomes: lipase increased (PT, severe AEs [CTCAE grade ≥ 3]), amylase increased (PT, severe AEs [CTCAE grade ≥ 3]), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]), and endocrine disorders (SOC, severe AEs [CTCAE grade ≥ 3]). In each case, there was a hint of greater harm from nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy.

2.2.1 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- sex (male versus female)
- age (< 65 years versus ≥ 65 years)
- brain metastases at baseline (yes versus no)
- tumour histology (squamous vs. non-squamous)

No interaction tests and subgroup analyses are available for the following outcomes: EQ-5D VAS (response threshold of 15 points), discontinuation due to AEs (discontinuation of at least

one drug component), immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3). Furthermore, Kaplan-Meier curves for the subgroup analyses are missing.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup. The results are presented in Table 7.

Table 7: Subgroups (mortality, side effects) – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%)

Study Outcome Characteristic Subgroup	Nivolumab + ipilimumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[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[c]
Study CA209-9LA						
Overall survival						
Brain metastases at baseline						
Yes	45	NA [12.39; NC] 20 (44.4)	35	7.82 [5.26; 10.74] 29 (82.9)	0.35 [0.19; 0.61]	< 0.001
No	217	15.44 [13.67; 20.53] 117 (53.9)	200	10.73 [8.97; 13.08] 138 (69.0)	0.68 [0.53; 0.87]	0.002
Total					Interaction[d]:	0.035
Specific AEs: anaemia (PT, severe AEs[e])						
Tumour histology						
Squamous	80	NA 10 (12.5)	74	NA 6 (8.1)	1.42 [0.51; 3.97]	0.5055
Non-squamous	180	NA 12 (6.7)	153	NA 33 (21.6)	0.29 [0.15; 0.56]	< 0.001
Total					Interaction[d]:	0.009

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. Effect and CI: unstratified Cox proportional hazards model.
c. p-value: unstratified log-rank test.
d. Interaction: from unstratified Cox proportional hazards model with the factors treatment group, subgroup and interaction term for treatment group*subgroup.
e. Operationalized as CTCAE grade ≥ 3.

CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; RCT randomized controlled trial

Mortality

Overall survival

There was an effect modification by the characteristic “brain metastases at baseline” for the outcome “overall survival”.

For both patients with and patients without brain metastases, there was a statistically significant difference in favour of nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy. For both subgroups, this resulted in an indication of an added benefit of nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy, but with different extents.

Side effects

Anaemia (PT, severe AEs [CTCAE grade ≥ 3])

There was an effect modification by the characteristic "tumour histology" for the outcome "anaemia" (PT, severe AEs [CTCAE grade ≥ 3]).

For patients with non-squamous histology, there was a statistically significant difference in favour of nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy. For patients with non-squamous histology, this resulted in a hint of lesser harm from nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy. For patients with squamous histology, in contrast, there was no difference between the treatment groups. This resulted in no hint of lesser or greater harm from nivolumab + ipilimumab + platinum-based chemotherapy for patients with squamous histology, lesser or greater harm is therefore not proven.

2.3 Probability and extent of added benefit

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.2 (see Table 8).

Determination of the outcome category for the outcome "discontinuation due to AEs" (discontinuation of at least one drug component)

It cannot be inferred from the dossier for the following outcome whether it is serious/severe or non-serious/non-severe. The classification for this outcome is justified.

For the subpopulation with PD-L1 expression < 50%, the company only presented analyses at SOC and PT level separately according to CTCAE grade for the discontinuation of all drug components due to AEs. In its comments, the company subsequently submitted analyses at SOC or PT level separately according to CTCAE grade for the discontinuation of at least one drug component due to AEs for the subgroup of squamous and non-squamous histology [3].

However, these analyses also include the events that can be attributed to progression of the underlying disease. Under the conservative assumption that all progression events included in the analyses had CTCAE grade ≥ 3, > 50% of the events of the outcome "discontinuation of at least one drug component due to AEs" still had CTCAE grade ≥ 3. The outcome "discontinuation due to AEs" (discontinuation of at least one drug component) was therefore assigned to the outcome category "serious/severe".

Table 8: Extent of added benefit at outcome level: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab + chemotherapy[a] vs. chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival Brain metastases at baseline Yes	NA vs. 7.82 HR: 0.35 [0.19; 0.61] p < 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
No	15.44 vs. 10.73 HR: 0.68 [0.53; 0.87] p = 0.002 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
Symptoms (LCSS ASBI; definitive deterioration of 15 points)	NA vs. NA HR: 0.78 [0.47; 1.29] p = 0.330	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS; definitive deterioration of 15 points)	22.21 vs. 17.81 HR: 0.75 [0.52; 1.09] p = 0.127	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcomes from this category were not recorded		
Side effects		
SAEs	5.09 vs. 11.17 HR: 1.52 [1.18; 1.95] HR: 0.66 [0.51; 0.85][d] p = 0.001 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Severe AEs	2.83 vs. 3.71 HR: 1.27 [1.02; 1.58] HR: 0.79 [0.63; 0.98][d] p = 0.031 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Discontinuation due to AEs (discontinuation of at least one drug component)	NA vs. NA HR: 1.98 [1.31; 2.99] HR: 0.51 [0.33; 0.76][d] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"

Table 8: Extent of added benefit at outcome level: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab + chemotherapy[a] vs. chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Immune-related SAEs	NA vs. NA HR: 3.27 [1.82; 5.88] HR: 0.31 [0.17; 0.55][d] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Immune-related severe AEs	NA vs. NA HR: 2.94 [1.81; 4.79] HR: 0.34 [0.21; 0.55][d] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Anaemia (severe AEs) Tumour histology Squamous	NA vs. NA HR: 1.42 [0.51; 3.97] p = 0.5055	Greater/lesser harm not proven
Non-squamous	NA vs. NA HR: 0.29 [0.15; 0.56] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: "major"
Lipase increased (severe AEs)	NA vs. NA HR: 4.75 [1.40; 16.05] HR: 0.21 [0.06; 0.71][d] p = 0.006 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Amylase increased (severe AEs)	NA HR: NC[e] p = 0.006 Probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"
Hepatobiliary disorders (severe AEs)	NA vs. NA HR: NC[e] p = < 0.001 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"
Skin and subcutaneous tissue disorders (severe AEs)	NA vs. NA HR: 4.80 [1.40; 16.40] HR: 0.21 [0.06; 0.71][d] p = 0.006 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"

Table 8: Extent of added benefit at outcome level: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab + chemotherapy[a] vs. chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Endocrine disorders (severe AEs)	NA vs. NA HR: NC[e] p = 0.006 Probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. Since no events occurred in one study arm, the HR cannot be estimated.

AE: adverse event; ASBI: average symptom burden index; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; SAE: serious adverse event; VAS: visual analogue

Overall conclusion on added benefit

Table 9 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 9: Positive and negative effects from the assessment of nivolumab + ipilimumab + platinum-based chemotherapy[a] in comparison with platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%)

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ Patients with brain metastases at baseline indication of an added benefit – extent: "major" ▫ Patients without brain metastases at baseline indication of an added benefit – extent: "considerable"	–
Serious/severe side effects ▪ Non-squamous tumour histology ▫ Anaemia (severe AEs): Hint of lesser harm – extent "major"	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "considerable" ▫ Immune-related SAEs: hint of greater harm – extent: "major" ▪ Discontinuation due to AEs (discontinuation of at least one drug component): hint of greater harm – extent: "considerable" ▪ Severe AEs: hint of greater harm – extent: "minor" ▫ Immune-related severe AEs: hint of greater harm – extent "major" ▫ Lipase increased (severe AEs): hint of greater harm – extent: "major" ▫ Amylase increased (severe AEs): hint of greater harm – extent: "non-quantifiable" ▫ Hepatobiliary disorders (severe AEs): hint of greater harm – extent: "non-quantifiable" ▫ Skin and subcutaneous tissue disorders (severe AEs): hint of greater harm – extent: "major" ▫ Endocrine disorders (severe AEs): hint of greater harm – extent: "non-quantifiable"
Data on health-related quality of life were not recorded.	
a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel. AE: adverse event; PD-L1: programmed cell death ligand 1; SAE: serious adverse event	

The overall picture shows 2 positive (partly only in subgroups) as well as numerous negative effects of nivolumab + ipilimumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy. Due to the relevant effect modification by the characteristic "brain metastases at baseline" in the outcome "overall survival", the added benefit is derived separately for these subgroups.

On the side of positive effects, there is an indication of major added benefit in patients with brain metastases, and an indication of considerable added benefit in patients without brain metastases for the outcome "overall survival". In addition, there is a hint of lesser harm with the extent "major" for patients with non-squamous histology for the specific severe AE "anaemia".

On the side of negative effects, there is a hint of greater harm with the extent "minor" or "considerable" for each of the outcomes "severe AEs", "SAEs" and "discontinuation due to AEs". In addition, there are several negative effects, each with the probability "hint", partly with major extent, in specific AEs.

Overall, the numerous negative effects do not completely outweigh the advantage in overall survival, but result in a subgroup-specific downgrading of the extent of the added benefit. The advantage for the specific severe AE "anaemia" in patients with non-squamous histology does not have a relevant impact on the added benefit.

In summary, there is therefore an indication of a considerable added benefit of nivolumab + ipilimumab + platinum-based chemotherapy in comparison with the appropriate comparator therapy (ACT) in the first-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression < 50% for patients with brain metastases. For patients without brain metastases, there is an indication of a minor added benefit of nivolumab + ipilimumab + platinum-based chemotherapy in comparison with the ACT.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of nivolumab + ipilimumab + platinum-based chemotherapy from dossier assessment A20-118 for research question 2: There is an indication of a considerable added benefit for patients with brain metastases at baseline and an indication of a minor added benefit for patients without brain metastases at baseline. This differs from the initial assessment, in which a non-quantifiable added benefit was derived exclusively for patients with non-squamous histology. For research question 1, there is no change in comparison with dossier assessment A20-118.

The following Table 10 shows the result of the benefit assessment of nivolumab + ipilimumab + platinum-based chemotherapy under consideration of dossier assessment A20-118 and the present addendum.

Table 10: Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Subindication	ACT[a]	Probability and extent of added benefit[b]
1	First-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation in adults with PD-L1 expression (TPS) ≥ 50%[c]	Pembrolizumab as monotherapy	Added benefit not proven
2	First-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation in adults with PD-L1 expression (TPS) < 50%[c]	▪ **Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed [except in mainly squamous histology]) *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed [except in mainly squamous histology]); see Appendix VI to Section K of the Pharmaceutical Directive *or* ▪ carboplatin in combination with nab-paclitaxel *or* ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology) *or* ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology)	▪ Patients with brain metastases ▫ **indication of an added benefit; extent: "considerable"[d]** ▪ Patients without brain metastases ▫ **indication of an added benefit; extent: "minor"[d]**

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Changes in comparison with dossier assessment A20-118 are printed in **bold**.
c. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
d. Only patients with an ECOG PS of 0 or 1 were included in the CA209-9LA study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TPS: Tumour Proportion Score

The G-BA decides on the added benefit.

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Appendix A – Kaplan-Meier curves

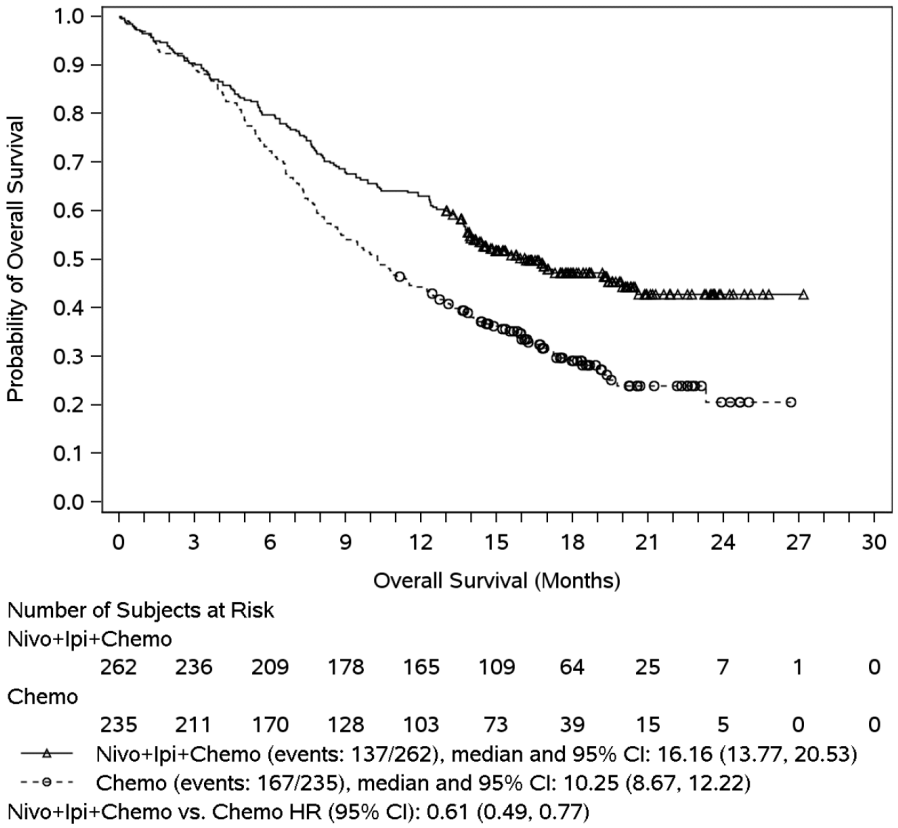

Figure 1: Kaplan-Meier curve for the outcome "overall survival" (study CA209 9LA, research question 2: PD L1 expression < 50%)

No Kaplan-Meier curves are available for the outcome "overall survival", separated by brain metastases at baseline (yes versus no).

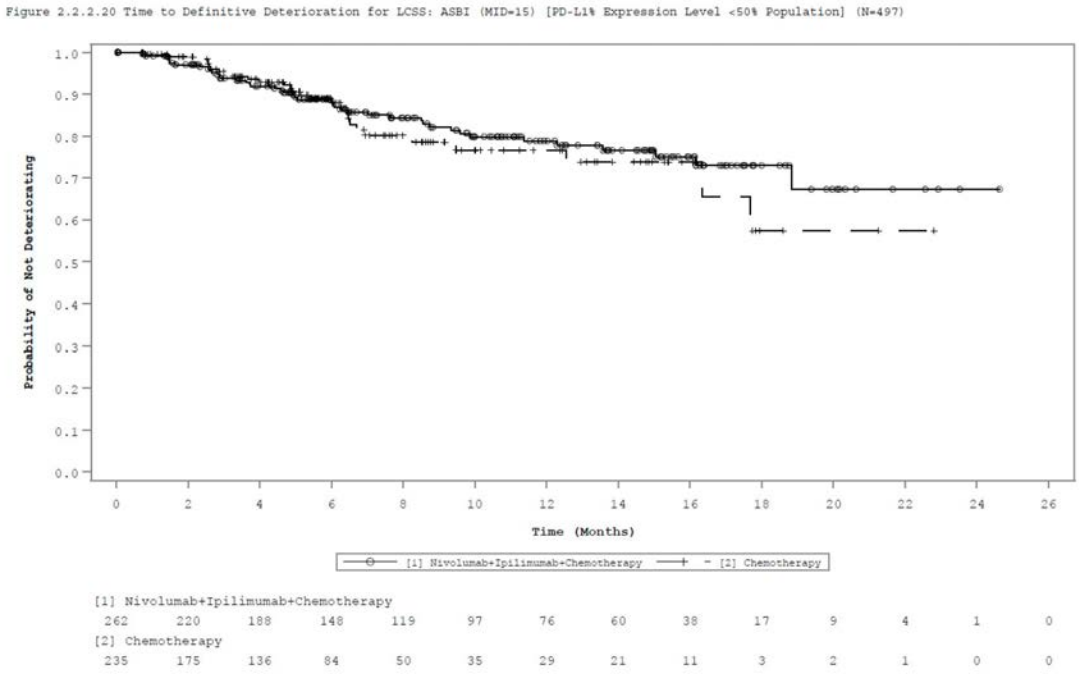

Figure 2: Kaplan-Meier curve for the outcome "LCSS ASBI", definitive deterioration of 15 points (study CA209-9LA, research question 2: PD-L1 expression < 50%)

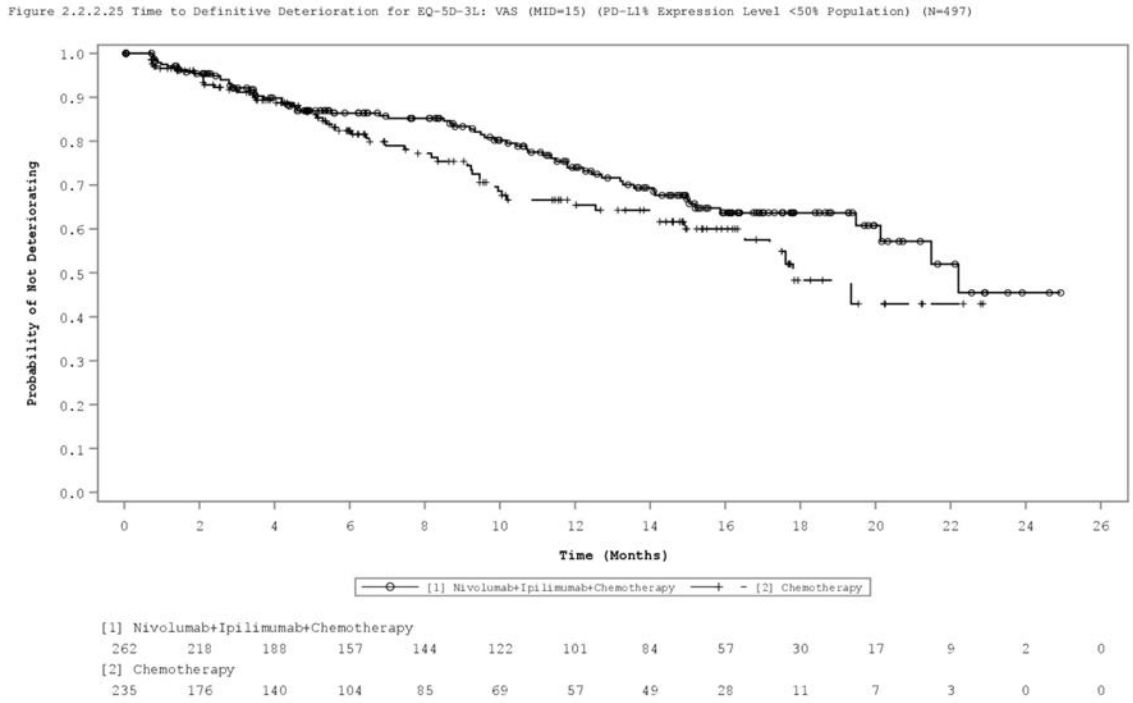

Figure 3: Kaplan-Meier curve for the outcome "EQ-5D VAS", definitive deterioration of 15 points (study CA209-9LA, research question 2: PD-L1 expression < 50%)

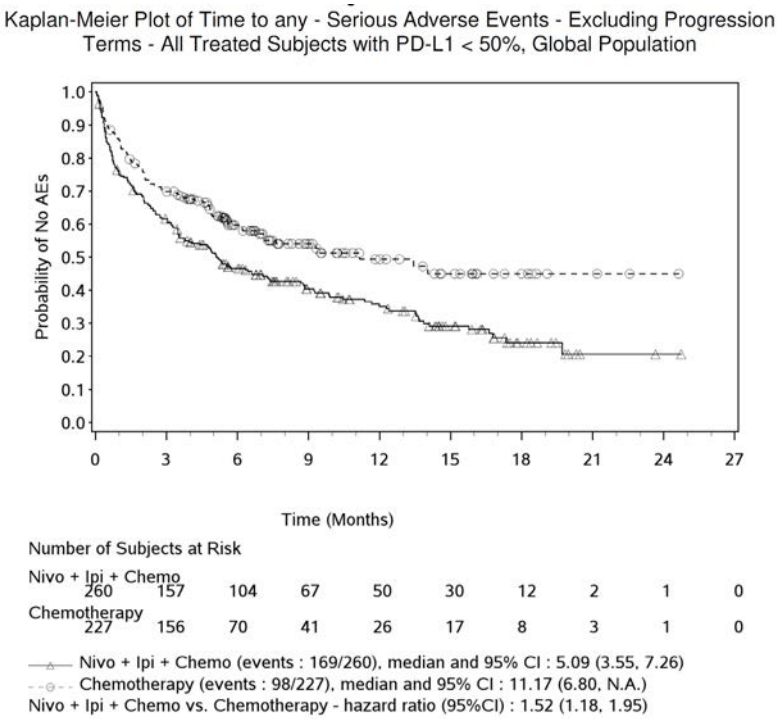

Figure 4: Kaplan-Meier curve for the outcome "SAEs" (study CA209-9LA, research question 2: PD-L1 expression < 50%)

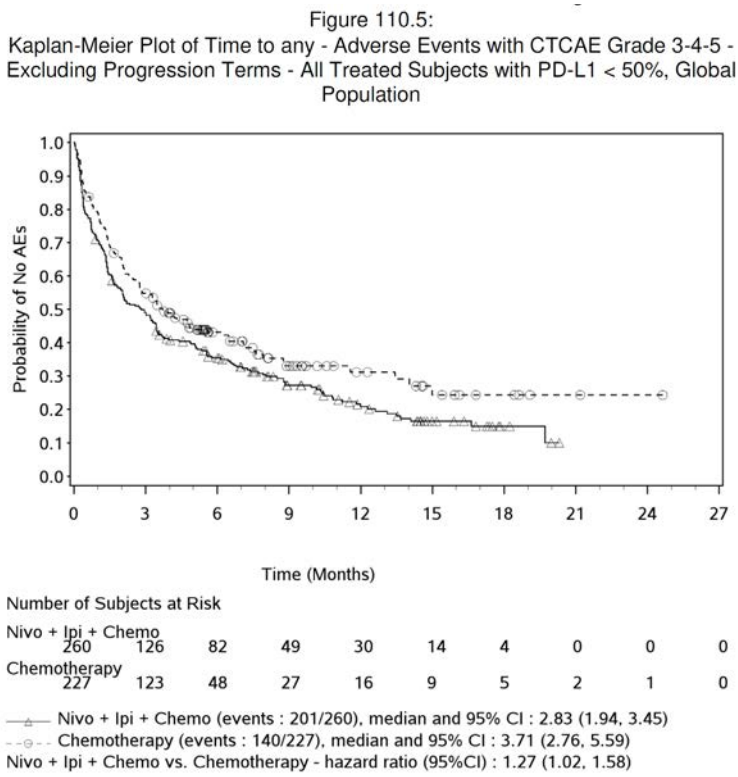

Figure 5: Kaplan-Meier curve for the outcome "severe AEs with CTCAE grade ≥ 3" (study CA209-9LA, research question 2: PD-L1 expression < 50%)

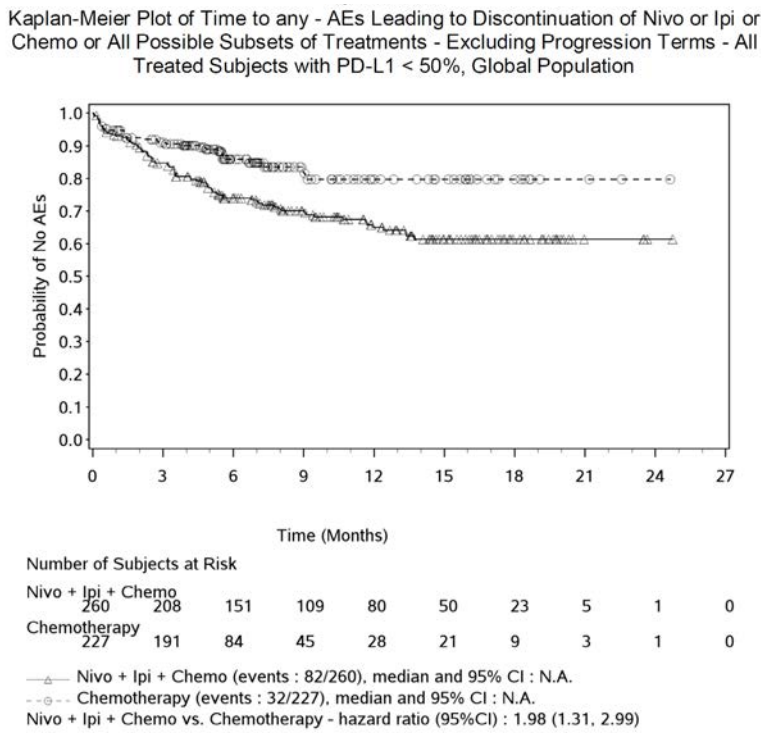

Figure 6: Kaplan-Meier curve for the outcome “discontinuation due to AEs” (discontinuation of at least one drug component) (study CA209-9LA, research question 2: PD-L1 expression < 50%)

Appendix B – Subsequent therapies

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (study CA209-9LA) (multipage table)

Study **Regimen** **Drug class** **Drug**	**Patients with subsequent therapy n (%)[b]**	
	Intervention **N = 262**	**Comparison** **N = 235**
CA209-9LA		
Total	94 (35.9)	108 (46.0)
Subsequent radiotherapy	31 (11.8)	34 (14.5)
Curative radiotherapy	1 (0.4)	0
Radiotherapy allowed during treatment	29 (11.1)	34 (14.5)
Other	2 (0.8)	0
Subsequent surgical intervention	2 (0.8)	0
Subsequent systemic therapy	81 (30.9)	96 (40.9)
Immunotherapy	13 (5.0)	68 (28.9)
Anti-PD-1	6 (2.3)	52 (22.1)
Nivolumab	3 (1.1)	37 (15.7)
Pembrolizumab	3 (1.1)	15 (6.4)
Anti-PD-L1	3 (1.1)	14 (6.0)
Atezolizumab	3 (1.1)	13 (5.5)
Durvalumab	0	1 (0.4)
Anti-CTLA-4	0	1 (0.4)
Ipilimumab	0	1 (0.4)
Other immunotherapy	4 (1.5)	7 (3.0)
Canakinumab/placebo	2 (0.8)	0
Canakinumab	1 (0.4)	0
EC ABBV-181	1 (0.4)	0
EC ABBV-927	1 (0.4)	0
AMG510	0	1 (0.4)
ANTI CD44 (investigational product)	0	1 (0.4)
Immunotherapy	0	1 (0.4)
Experimental immunotherapy/placebo	0	2 (0.9)
Experimental drug (ADXS-503)	0	1 (0.4)
JNJ-757	0	1 (0.4)
Targeted therapy	15 (5.7)	10 (4.3)
ALK/EGFR tyrosine kinase inhibitors	2 (0.8)	4 (1.7)
Afatinib	2 (0.8)	2 (0.9)
Crizotinib	0	1 (0.4)
Erlotinib	0	1 (0.4)
VEGFR inhibitors	13 (5.0)	7 (3.0)
Bevacizumab	8 (3.1)	1 (0.4)

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (study CA209-9LA) (multipage table)

Study	**Patients with subsequent therapy n (%)[b]**	
Regimen **Drug class** **Drug**	**Intervention** **N = 262**	**Comparison** **N = 235**
Ramucirumab	3 (1.1)	6 (2.6)
Cabozantinib	2 (0.8)	0
Docetaxel; ramucirumab	1 (0.4)	1 (0.4)
Experimental drugs	1 (0.4)	3 (1.3)
B0112	1 (0.4)	0
AZD 6738	0	1 (0.4)
GSK 3359609	0	1 (0.4)
LY 3300054	0	1 (0.4)
LY 3321367	0	1 (0.4)
Chemotherapy	78 (29.8)	56 (23.8)
Carboplatin	43 (16.4)	8 (3.4)
Docetaxel	32 (12.2)	32 (13.6)
Pemetrexed[c]	24 (9.2)	4 (1.7)
Paclitaxel	17 (6.5)	7 (3.0)
Gemcitabine	13 (5.0)	10 (4.3)
Cisplatin	8 (3.1)	3 (1.3)
Vinorelbine	4 (1.5)	3 (1.3)
Gemcitabine	2 (0.8)	3 (1.3)
Nintedanib esilate[c]	2 (0.8)	0
Nab-paclitaxel	2 (0.8)	2 (0.9)
Vinorelbine	2 (0.8)	4 (1.7)
Amrubicin	1 (0.4)	0
Etoposide	1 (0.4)	0
Gimeracil; oteracil; tegafur	1 (0.4)	3 (1.3)
Nintedanib[c]	1 (0.4)	3 (1.3)
Pemetrexed disodium[c]	1 (0.4)	0
Galunisertib	0	2 (0.9)

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. The percentages refer to the ITT population.
c. It is unclear why the company lists pemetrexed and nintedanib twice.

ALK: anaplastic lymphoma kinase; CTLA-4: cytotoxic T-lymphocyte-associated antigen-4; EGFR: epidermal growth factor receptor; ITT: intention to treat; n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death protein; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; VEGFR: vascular endothelial growth factor receptor

Appendix C – Results on side effects

Table 12: Common AEs[a] – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[b] (research question 2: PD-L1 expression < 50%) (multipage table)

Study	Patients with event n (%)	
SOC[c] PT[c]	Nivolumab + ipilimumab + platinum-based chemotherapy[b] N = 260	Platinum-based chemotherapy[b] N = 227
CA209-9LA		
Overall AE rate[d]	260 (100)	222 (97.8)
General disorders and administration site conditions	202 (77.7)	135 (59.5)
Asthenia	86 (33.1)	56 (24.7)
Fatigue	60 (23.1)	43 (18.9)
Pyrexia	40 (15.4)	20 (8.8)
Oedema peripheral	21 (8.1)	19 (8.4)
Mucosal inflammation	18 (6.9)	9 (4.0)
Malaise	15 (5.8)	10 (4.4)
Chest pain	13 (5.0)	5 (2.2)
Non-cardiac chest pain	13 (5.0)	11 (4.8)
Gastrointestinal disorders	187 (71.9)	150 (66.1)
Nausea	89 (34.2)	93 (41.0)
Diarrhoea	85 (32.7)	50 (22.0)
Constipation	61 (23.5)	54 (23.8)
Vomiting	52 (20.0)	38 (16.7)
Abdominal pain	20 (7.7)	18 (7.9)
Abdominal pain upper	16 (6.2)	12 (5.3)
Dry mouth	11 (4.2)	0 (0)
Stomatitis	9 (3.5)	11 (4.8)
Metabolism and nutrition disorders	152 (58.5)	103 (45.4)
Decreased appetite	78 (30.0)	58 (25.6)
Hyponatraemia	26 (10.0)	14 (6.2)
Hyperglycaemia	19 (7.3)	20 (8.8)
Hypomagnesaemia	19 (7.3)	17 (7.5)
Dehydration	18 (6.9)	8 (3.5)
Hypoalbuminaemia	14 (5.4)	19 (8.4)
Hypokalaemia	13 (5.0)	10 (4.4)
Hypophosphataemia	11 (4.2)	6 (2.6)
Respiratory, thoracic and mediastinal disorders	139 (53.5)	91 (40.1)
Dyspnoea	50 (19.2)	36 (15.9)
Cough	48 (18.5)	25 (11.0)

Table 12: Common AEs[a] – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[b] (research question 2: PD-L1 expression < 50%) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] PT[c]	**Nivolumab + ipilimumab + platinum-based chemotherapy[b] N = 260**	**Platinum-based chemotherapy[b] N = 227**
Pneumonitis	18 (6.9)	5 (2.2)
Haemoptysis	14 (5.4)	8 (3.5)
Respiratory failure	11 (4.2)	3 (1.3)
Hiccups	7 (2.7)	11 (4.8)
Skin and subcutaneous tissue disorders	136 (52.3)	58 (25.6)
Pruritus	58 (22.3)	9 (4.0)
Rash	48 (18.5)	10 (4.4)
Alopecia	31 (11.9)	22 (9.7)
Rash maculo-papular	17 (6.5)	5 (2.2)
Dry skin	13 (5.0)	4 (1.8)
Musculoskeletal and connective tissue disorders	125 (48.1)	71 (31.3)
Arthralgia	41 (15.8)	18 (7.9)
Back pain	41 (15.8)	21 (9.3)
Myalgia	20 (7.7)	7 (3.1)
Pain in extremity	16 (6.2)	8 (3.5)
Musculoskeletal pain	13 (5.0)	5 (2.2)
Infections and infestations	124 (47.7)	86 (37.9)
Pneumonia	29 (11.2)	22 (9.7)
Bronchitis	20 (7.7)	8 (3.5)
Respiratory tract infection	14 (5.4)	6 (2.6)
Urinary tract infection	13 (5.0)	7 (3.1)
Upper respiratory tract infection	12 (4.6)	5 (2.2)
Conjunctivitis	11 (4.2)	6 (2.6)
Blood and lymphatic system disorders	118 (45.4)	130 (57.3)
Anaemia	87 (33.5)	99 (43.6)
Neutropenia	34 (13.1)	38 (16.7)
Thrombocytopenia	15 (5.8)	26 (11.5)
Febrile neutropenia	13 (5.0)	6 (2.6)
Leukopenia	5 (1.9)	11 (4.8)
Investigations	118 (45.4)	73 (32.2)
Lipase increased	28 (10.8)	4 (1.8)
Amylase increased	25 (9.6)	6 (2.6)
Alanine aminotransferase increased	23 (8.8)	14 (6.2)
Weight decreased	23 (8.8)	15 (6.6)

Table 12: Common AEs[a] – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[b] (research question 2: PD-L1 expression < 50%) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] PT[c]	**Nivolumab + ipilimumab + platinum-based chemotherapy[b] N = 260**	**Platinum-based chemotherapy[b] N = 227**
Aspartate aminotransferase increased	21 (8.1)	7 (3.1)
Blood creatinine increased	17 (6.5)	15 (6.6)
Blood alkaline phosphatase increased	16 (6.2)	10 (4.4)
Neutrophil count decreased	13 (5.0)	9 (4.0)
White blood cell count decreased	10 (3.8)	5 (2.2)
Platelet count decreased	9 (3.5)	12 (5.3)
Nervous system disorders	88 (33.8)	83 (36.6)
Headache	26 (10.0)	21 (9.3)
Dizziness	16 (6.2)	15 (6.6)
Dysgeusia	11 (4.2)	11 (4.8)
Peripheral neuropathy	7 (2.7)	10 (4.4)
Paraesthesia	6 (2.3)	10 (4.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	66 (25.4)	55 (24.2)
Malignant neoplasm progression	48 (18.5)	49 (21.6)
Endocrine disorders	63 (24.2)	10 (4.4)
Hypothyroidism	42 (16.2)	7 (3.1)
Hyperthyroidism	23 (8.8)	2 (0.9)
Adrenal insufficiency	11 (4.2)	1 (0.4)
Psychiatric disorders	49 (18.8)	27 (11.9)
Insomnia	18 (6.9)	10 (4.4)
Anxiety	14 (5.4)	6 (2.6)
Renal and urinary disorders	36 (13.8)	19 (8.4)
Vascular disorders	35 (13.5)	20 (8.8)
Hypertension	11 (4.2)	5 (2.2)
Cardiac disorders	33 (12.7)	17 (7.5)
Hepatobiliary disorders	33 (12.7)	4 (1.8)
Hepatotoxicity	10 (3.8)	1 (0.4)
Eye disorders	27 (10.4)	21 (9.3)
Injury, poisoning and procedural complications	24 (9.2)	12 (5.3)
Ear and labyrinth disorders	16 (6.2)	7 (3.1)
Vertigo	10 (3.8)	5 (2.2)
Immune system disorders	10 (3.8)	3 (1.3)
Reproductive system and breast disorders	10 (3.8)	8 (3.5)

Table 12: Common AEs[a] – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[b] (research question 2: PD-L1 expression < 50%) (multipage table)

Study	Patients with event n (%)	
SOC[c] PT[c]	Nivolumab + ipilimumab + platinum-based chemotherapy[b] N = 260	Platinum-based chemotherapy[b] N = 227

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
c. MedDRA version 22.1. SOC and PT from MedDRA without adaptation.
d. AEs including events caused by progression of the underlying disease.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 13: Common SAEs[a] – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[b] (research question 2: PD-L1 expression < 50%)

Study	**Patients with event n (%)**	
SOC[c] PT[c]	**Nivolumab + ipilimumab + platinum-based chemotherapy[b] N = 260**	**Platinum-based chemotherapy[b] N = 227**
CA209-9LA		
Total SAE rate[d]	188 (72.3)	121 (53.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	57 (21.9)	51 (22.5)
Malignant neoplasm progression	47 (18.1)	48 (21.1)
Infections and infestations	52 (20.0)	34 (15.0)
Pneumonia	22 (8.5)	15 (6.6)
Respiratory, thoracic and mediastinal disorders	41 (15.8)	25 (11.0)
Pneumonitis	11 (4.2)	4 (1.8)
Respiratory failure	11 (4.2)	2 (0.9)
Gastrointestinal disorders	27 (10.4)	15 (6.6)
Diarrhoea	10 (3.8)	3 (1.3)
Blood and lymphatic system disorders	24 (9.2)	20 (8.8)
Febrile neutropenia	10 (3.8)	6 (2.6)
General disorders and administration site conditions	19 (7.3)	13 (5.7)
Nervous system disorders	18 (6.9)	8 (3.5)
Hepatobiliary disorders	16 (6.2)	0 (0)
Cardiac disorders	15 (5.8)	8 (3.5)
Metabolism and nutrition disorders	14 (5.4)	5 (2.2)
Musculoskeletal and connective tissue disorders	13 (5.0)	4 (1.8)
Renal and urinary disorders	13 (5.0)	7 (3.1)
Endocrine disorders	12 (4.6)	0 (0)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
c. MedDRA version 22.1. SOC and PT from MedDRA without adaptation.
d. AEs including events caused by progression of the underlying disease.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 14: Common severe AEs[a] (CTCAE ≥ 3) – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[b]; non-squamous histology (research question 2: PD-L1 expression < 50%) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] PT[c]	**Nivolumab + ipilimumab + platinum-based chemotherapy[b] N = 260**	**Platinum-based chemotherapy[b] N = 227**
CA209-9LA		
Overall rate of severe AEs (CTCAE grade ≥ 3)[d]	213 (81.9)	155 (68.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	57 (21.9)	51 (22.5)
Malignant neoplasm progression	47 (18.1)	48 (21.1)
Blood and lymphatic system disorders	54 (20.8)	63 (27.8)
Neutropenia	24 (9.2)	20 (8.8)
Anaemia	22 (8.5)	39 (17.2)
Febrile neutropenia	13 (5.0)	5 (2.2)
Thrombocytopenia	10 (3.8)	9 (4.0)
Investigations	53 (20.4)	18 (7.9) 209
Lipase increased	21 (8.1)	3 (1.3)
Amylase increased	10 (3.8)	0 (0)
Neutrophil count decreased	10 (3.8)	5 (2.2)
Respiratory, thoracic and mediastinal disorders	44 (16.9)	28 (12.3)
Dyspnoea	14 (5.4)	12 (5.3)
Respiratory failure	10 (3.8)	2 (0.9)
Metabolism and nutrition disorders	43 (16.5)	21 (9.3)
Hyponatraemia	17 (6.5)	7 (3.1)
Infections and infestations	41 (15.8)	31 (13.7)
Pneumonia	16 (6.2)	16 (7.0)
General disorders and administration site conditions	36 (13.8)	27 (11.9)
Asthenia	11 (4.2)	12 (5.3)
Gastrointestinal disorders	33 (12.7)	20 (8.8)
Diarrhoea	14 (5.4)	5 (2.2)
Cardiac disorders	19 (7.3)	11 (4.8)
Hepatobiliary disorders	18 (6.9)	0 (0)
Skin and subcutaneous tissue disorders	17 (6.5)	3 (1.3)
Musculoskeletal and connective tissue disorders	15 (5.8)	10 (4.4)
Vascular disorders	15 (5.8)	8 (3.5)
Nervous system disorders	12 (4.6)	6 (2.6)

Table 14: Common severe AEs[a] (CTCAE ≥ 3) – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[b]; non-squamous histology (research question 2: PD-L1 expression < 50%) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] PT[c]	**Nivolumab + ipilimumab + platinum-based chemotherapy[b] N = 260**	**Platinum-based chemotherapy[b] N = 227**
Endocrine disorders	11 (4.2)	0 (0)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
c. MedDRA version 22.1. SOC and PT from MedDRA without adaptation.
d. AEs including events caused by progression of the underlying disease.

AE: adverse event; 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; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix D – Results on health status (EQ-5D VAS supplementary presentation)

Table 15: Results (morbidity, supplementary presentation) – RCT, direct comparison: nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%)

Study Outcome category Outcome	Nivolumab + ipilimumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Nivolumab + ipilimumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[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]
CA209-9LA					
Morbidity					
Health status (EQ-5D VAS)[c]					
7 points	262	15.87 [13.21; 19.29] 103 (39.3)	235	10.45 [9.03; 15.38] 89 (37.9)	0.68 [0.51; 0.91] 0.010
10 points	262	17.51 [14.13; 19.48] 95 (36.3%)	235	11.83 [9.26; NC] 82 (34.9%)	0.70 [0.52; 0.95]; 0.023

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. Effect and CI: presumably unstratified Cox proportional hazards model, log-log transformation (according to Brookmeyer and Crowley) with baseline values as covariates; p-value: presumably unstratified log-rank test.
c. Time to definitive deterioration; defined as a decrease in score by the response threshold without improvement below the response threshold in any of the subsequent recordings.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; VAS: visual analogue scale

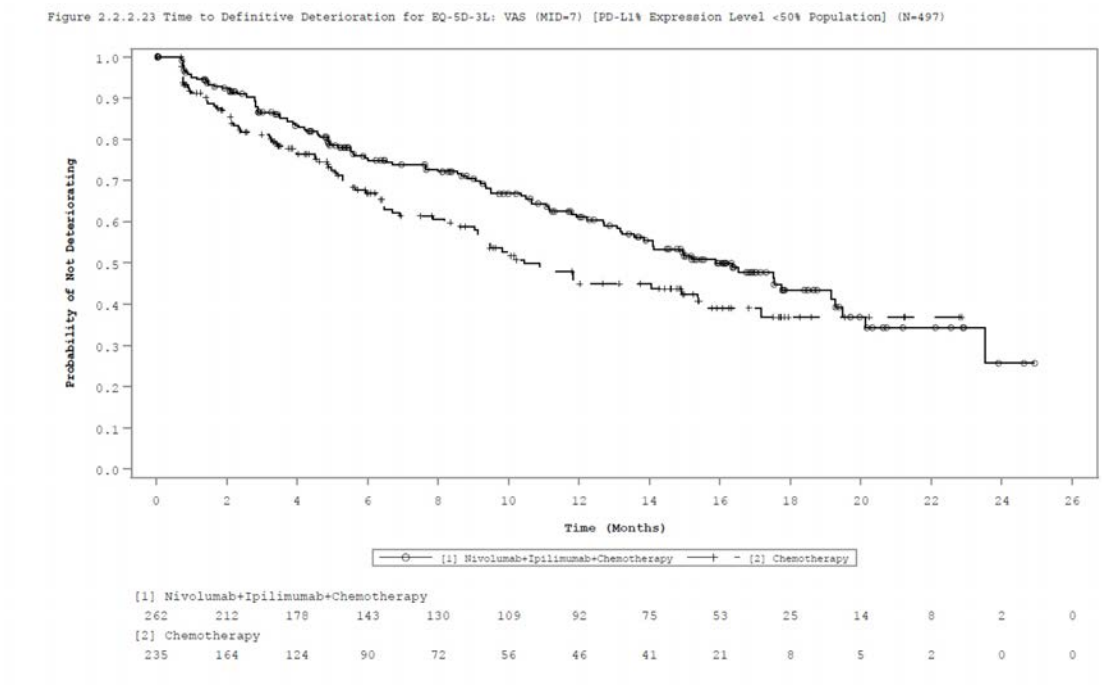

Figure 7: Kaplan-Meier curve for the outcome "EQ-5D VAS", definitive deterioration of 7 points (study CA209-9LA, research question 2: PD-L1 expression < 50%)

The company did not provide a Kaplan-Meier curve for the definitive deterioration of 10 points (EQ-5D VAS).