Nivolumab (NSCLC, neoadjuvant)

Addendum to Project A23-74 (dossier assessment)[1]

ADDENDUM

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Jana Göbel
- Charlotte Guddat
- Lisa Junge
- Prateek Mishra
- Volker Vervölgyi

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival (
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IASLC	International Association for the Study of Lung Cancer
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PT	Preferred Term
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 12 December 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-74 (Nivolumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the subsequent assessment of the CheckMate 816 study (programmed cell death ligand 1 [PD-L1]-positive population) for the total population and for the population treated with cisplatin ("cisplatin population"), taking into account the information provided in the dossier [2] and the data subsequently submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [3].

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

As explained in detail in dossier assessment A23-74 [1], the analyses for the subpopulation with PD-L1 expression ≥ 1% (hereinafter referred to as "PD-L1-positive population") of the CheckMate 816 study, which compared nivolumab in combination with platinum-based chemotherapy (hereinafter referred to as "nivolumab + platinum-based chemotherapy") with platinum-based chemotherapy alone, presented by the company were not used for the benefit assessment, as the appropriate comparator therapy (ACT) was not implemented. The ACT specified by the G-BA is an individualized treatment selected from:

- Neoadjuvant systemic chemotherapy selected from
  - cisplatin in combination with vinorelbine

    and
  - cisplatin in combination with paclitaxel (only for patients in the advanced stage)

  and
- simultaneous radiochemotherapy with cisplatin in combination with vinorelbine as chemotherapy

taking into account tumour stage, presence/absence of Pancoast tumour, and feasibility of R0 resection.

The reasons given in the dossier assessment for the lack of implementation of the ACT were that all included patients received neoadjuvant systemic chemotherapy, (simultaneous radiochemotherapy was not offered in the study) and that an analysis of the intervention arm of the PD-L1-positive population versus the 7 patients (according to the company's comments) who received the combination of cisplatin + vinorelbine in the comparator arm of the PD-L1 population as part of individualized therapy according to the G-BA would not be appropriate, as this would violate the randomization. According to the European Public Assessment Report (EPAR), in contrast to the platinum component, the combination partner was assigned by the investigator only after randomization. The second aspect was ultimately decisive for not including the results of the CheckMate 816 study. Overall, the points of criticism listed in the dossier assessment remain valid, as does the assessment already made that the implementation of the ACT specified by the G-BA was inadequate.

In compliance with the commission, the results of the CheckMate 816 study are presented below for the PD-L1-positive population and for patients with PD-L1 expression ≥-1% who received cisplatin as a platinum component at the start of the study (hereinafter referred to as "cisplatin population"). The results for the PD-L1-positive population are described in Section 2.1, the results for the cisplatin population in Section 2.2.

2.1 Patients with tumour cell PD-L1 expression ≥ 1% (PD-L1-positive population)

2.1.1 Study characteristics

A detailed characterization of the CheckMate 816 study can be found in dossier assessment A23-74 [1] and its Appendix B.

Planned duration of follow-up observation

Table 1 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 1: Planned duration of follow-up observation – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b]

Study Outcome category Outcome	Planned follow-up observation
CheckMate 816	
Mortality	
Overall survival	Until death, end of study, or withdrawal of consent
Morbidity	
Failure of the curative approach[c]	Until occurrence of an event relevant to the outcome, or until the end of study, or withdrawal of consent
Health status (EQ-5D VAS)	Until death, end of study, or withdrawal of consent
Health-related quality of life	Outcome not recorded
Side effects	
All outcomes in the side effects category	For patients without adjuvant therapy: up to 100 days after neoadjuvant therapy or up to 90 days after surgery (whichever is longer) For patients with adjuvant therapy: up to 30 days after adjuvant therapy

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Includes the following events: disease progression, AE or any other event that precludes surgery; failed R0 resection of the tumour (R1, R2, Rx); recurrence after successful R0 resection; recurrence in patients without surgery; death from any cause.

AE: adverse event; RCT: randomized controlled trial; VAS: visual analogue scale

In the CheckMate 816 study, the outcomes of overall survival, failure of the curative approach, and health status were recorded until death, end of the study or withdrawal of consent.

The observation periods for the side effects outcomes are systematically shortened in the CheckMate 816 study, as they were only recorded up to 100 days after neoadjuvant therapy, up to 90 days after surgery, or up to 30 days after adjuvant therapy. In the CheckMate 816 study, optional adjuvant chemotherapy was possible after surgery (see below). However, drawing a reliable conclusion on the total study period or the time to patient death would require recording these outcomes for the total period, as was done for survival and the morbidity outcomes.

Characteristics of the PD-L1-positive population

Table 2 shows the characteristics of the PD-L1-positive population in the CheckMate 816 study.

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population) (multipage table)

Study Characteristic **Category**	**Nivolumab + platinum-based chemotherapy[a]** **N = 89**	**Platinum-based chemotherapy[b]** **N = 89**
CheckMate 816		
Age [years], mean (SD)	64 (8)	64 (9)
Sex according to CRF [F/M], %	26/74	27/73
ECOG Performance Status, n (%)		
0	67 (75)	63 (71)
≥ 1	22 (25)	26 (29)
Family origin, n (%)		
White	38 (43)	36 (40)
African American	1 (1)	1 (1)
Asian	50 (56)	52 (58)
Region, n (%)		
North America	16 (18)	21 (24)
Europe	19 (21)	11 (12)
Asia	50 (56)	52 (58)
Rest of the world	4 (4[c])	5 (6)
Smoking status, n (%)		
Never smoker	9 (10)	8 (9)
Smoker (current, former)	80 (90)	80 (90)
Unknown	0 (0)	1 (1)
Disease stage[d] at baseline according to CRF, n (%)		
Stage IB	7 (8)	2 (2)
Stage IIA	13 (15)	19 (21)
Stage IIB	12 (13[c])	11 (12)
Stage IIIA	56 (63)	56 (63)
Stage IV	1 (1)	1 (1)
PD-L1 status, n (%)		
1–49%	51 (57)	47 (53)
≥ 50%	38 (43)	42 (47)
Tumour histology, n (%)		
Squamous cell carcinoma	47 (53)	50 (56)
Non-squamous cell carcinoma	42 (47)	39 (44)

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population) (multipage table)

Study Characteristic Category	Nivolumab + platinum-based chemotherapy[a] N = 89	Platinum-based chemotherapy[b] N = 89
Type of platinum component, n (%)		
Cisplatin	61 (69)	66 (74)
Carboplatin	21 (24)	19 (21)
Switch from cisplatin to carboplatin	5 (6)	4 (4[c])
Not reported	2 (2)	0 (0)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)[e]	16 (18)	39 (44)

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Institute's calculation.
d. Staging according to IASLC, 7th edition [4].
e. Common reasons for study discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): death (14.6% vs. 34.8%) and withdrawal of consent (2.2% vs. 6.7%).

CRF: case report form; ECOG: Eastern Cooperative Oncology Group; F: female; IASLC: International Association for the Study of Lung Cancer; M: male; n: number of patients in the category; N: number of randomized patients in the relevant population; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

Both treatment arms are largely similar in terms of the demographic and clinical characteristics of the PD-L1-positive population in the CheckMate 816 study. The patients' mean age at study entry was 64 years, about 3 quarters of patients were male, and slightly less than half (43% and 40%) were of white family origin. An Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 was found in 75% and 71% of the patients. According to the 7th edition of the staging criteria of the International Association for the Study of Lung Cancer (IASLC) [4], the majority of patients (63%) were in stage IIIA. Patients in stage IB are not covered by the approval or the present research question. However, at 8% and 2% of patients respectively, this only affects a small proportion of the PD-L1-positive population.

No data are available on treatment discontinuation. The proportion of patients with study discontinuation was markedly higher in the control arm (44%) than in the intervention arm

(18%). The 2 most common reasons for study discontinuation were death and withdrawal of consent.

Information on the course of the study

Table 3 shows the median and mean treatment duration of the PD-L1-positive population and the median and mean observation period for the outcome of overall survival as well as the outcome categories of morbidity and side effects.

Table 3: Information on the course of the study – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population)

Study **Duration of the study phase** **Outcome category/outcome**	**Nivolumab + platinum-based chemotherapy[a]** **N = 89**	**Platinum-based chemotherapy[b]** **N = 89**
CheckMate 816		
Treatment duration[c] [months[d]]		
Median [min; max]	2.9 [1.4; 17.0][e]	3.1 [0.1; 15.2]
Mean (SD)	3.4 (2.3)[e]	3.9 (2.7)
Observation period [months[d]]		
Overall survival		
Median [min; max][f]	40.8 [2.7; 57.5]	37.9 [1.4; 53.9]
Mean (SD)[f]	38.3 (12.6)	32.8 (14.7)
Morbidity	ND	ND
Side effects		
Median[g] [min; max]	2.9 [ND]	3.1 [ND]
Mean (SD)	ND	ND

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Includes neoadjuvant and optional adjuvant study treatment.
d. Institute's calculation from weeks to months.
e. All patients who had received at least one dose of the study medication were included in the calculation (n = 88).
f. The observation period was presumably determined as the time from randomization until death or until the last data cut-off with database lock in October 2022.
g. No information on the calculation.

max: maximum; min: minimum; N: number of randomized patients; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

The treatment durations (including the neoadjuvant and the optional adjuvant study treatment) are comparable at 2.9 months in the intervention arm and 3.1 months in the control arm. The slightly longer treatment duration in the control arm presumably results from the notably higher proportion of adjuvant therapies in the control arm (see next section).

The median observation period for overall survival was 40.8 months in the intervention arm and 37.9 months in the control arm. No information is available on the observation period for the morbidity and side effects outcomes.

Information on adjuvant therapies

According to the study protocol, after surgery, patients could receive adjuvant chemotherapy consisting of up to 4 cycles of 3 weeks of chemotherapy and/or radiotherapy at the discretion of the investigator. The same 5 treatment regimens were available for adjuvant therapy as for neoadjuvant therapy in the comparator arm. These were cisplatin + gemcitabine (for squamous cell carcinoma), cisplatin + pemetrexed (for non-squamous cell carcinoma), cisplatin + vinorelbine, cisplatin + docetaxel, and carboplatin + paclitaxel.

Table 4 shows the available data on adjuvant therapies for patients in the PD-L1-positive population.

Table 4: Information on adjuvant therapies – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population)

Study **Drug class** **Drug**	**Patients with adjuvant therapy n (%)**	
	Nivolumab + platinum-based chemotherapy[a] **N = 89**	**Platinum-based chemotherapy[b]** **N = 89**
CheckMate 816		
Any adjuvant therapy	13 (14.6)	36 (40.4)
Systemic therapy	10 (11.2)	26 (29.2)
Radiotherapy	5 (5.6)	13 (14.6)
Radiotherapy without systemic therapy	3 (3.4)	10 (11.2)

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.

b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.

n: number of patients with adjuvant therapy; N: number of analysed patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

The available data on adjuvant therapy for the PD-L1-positive population shows that a notably higher proportion of patients received adjuvant therapy in the control arm (40.4%) than in the intervention arm (14.6%). The company did not provide any information on the proportions of patients who received the above-mentioned chemotherapy regimens.

The S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer [5] contains no information on the administration of adjuvant therapies following neoadjuvant treatment. For exclusively adjuvant therapy in first-line treatment, cisplatin-containing combinations over 4 cycles are recommended, with the greatest evidence in favour of the combination with vinorelbine [5,6]. For patients in stage IIIA with PD-L1 expression ≥ 50%, it is also recommended to offer additional adjuvant therapy with atezolizumab for 1 year after adjuvant chemotherapy. The extent to which these recommendations can be applied to a situation following prior neoadjuvant therapy is unclear.

Information on subsequent therapies

Table 5 shows the subsequent therapies patients of the PD-L1-positive population received after discontinuing the study medication.

Table 5: Information on subsequent antineoplastic therapies – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population) (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Nivolumab + platinum-based chemotherapy[a] **N = 89**	**Platinum-based chemotherapy[b]** **N = 89**
CheckMate 816		
Total[c]	22 (24.7)	43 (48.3)
Radiotherapy[d]	11 (12.4)	21 (23.6)
Surgical intervention[d]	3 (3.4)	3 (3.4)
First subsequent systemic therapy	18 (20.2)	36 (40.4)
Immunotherapy	3 (3.4)	22 (24.7)
Anti-PD-1	1 (1.1)	18 (20.2)
Nivolumab	0 (0)	1 (1.1)
Pembrolizumab	1 (1.1)	16 (18.0)
Toripalimab	0 (0)	1 (1.1)
Anti-PD-L1	2 (2.2)	3 (3.4)
Atezolizumab	1 (1.1)	0 (0)
Durvalumab	1 (1.1)	3 (3.4)
Other immunotherapy	0 (0)	1 (1.1)
Terelizumab	0 (0)	1 (1.1)
Targeted therapy	6 (6.7)	7 (7.9)
ALK/EGFR tyrosine kinase inhibitors	1 (1.1)	5 (5.6)
Alectinib	0 (0)	1 (1.1)
Gefitinib	0 (0)	2 (2.2)
Osimertinib	1 (1.1)	3 (3.4)
VEGF(R) inhibitors	5 (5.6)	3 (3.4)
Bevacizumab	2 (2.2)	1 (1.1)
Endostar	1 (1.1)	0 (0)
Endostatin	0 (0)	2 (2.2)
Ramucirumab	2 (2.2)	0 (0)

Table 5: Information on subsequent antineoplastic therapies – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population) (multipage table)

Study	**Patients with subsequent therapy n (%)**	
Drug class **Drug**	**Nivolumab + platinum-based chemotherapy[a]** **N = 89**	**Platinum-based chemotherapy[b]** **N = 89**
Other systemic cancer therapy (chemotherapy)	16 (18.0)	21 (23.6)
Carboplatin	6 (6.7)	10 (11.2)
Carboplatin/pembrolizumab/taxol	0 (0)	1 (1.1)
Cisplatin	4 (4.5)	4 (4.5)
Docetaxel	3 (3.4)	2 (2.2)
Etoposide	0 (0)	1 (1.1)
Gemcitabine	2 (2.2)	2 (2.2)
Lobaplatin	1 (1.1)	0 (0)
Nedaplatin	1 (1.1)	3 (3.4)
Paclitaxel	8 (9.0)	8 (9.0)
Pemetrexed	1 (1.1)	4 (4.5)
Vinorelbine	2 (2.2)	2 (2.2)
Other systemic cancer therapy	0 (0)	3 (3.4)
Herbal drugs	0 (0)	3 (3.4)

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Patients may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if patient was never treated), outside of the protocol-specified adjuvant therapy.
d. The line of therapy was not explicitly queried.

ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; VEGF(R): vascular endothelial growth factor receptor

According to the study protocol of the CheckMate 816 study, the choice of the subsequent antineoplastic therapies was not restricted. Overall, 22 (24.7%) patients in the intervention arm and 43 (48.3%) patients in the control arm received at least one subsequent antineoplastic therapy. In relation to the patients in whom an event-free survival (EFS) event other than death occurred (35 patients in the intervention arm versus 53 patients in the control arm, see Table 9), this means that 62.9% of the patients who were generally eligible

for subsequent therapy in the intervention arm and 81.1% in the control arm received at least one subsequent antineoplastic therapy.

In each study arm, 3 patients received subsequent surgery. The proportion of subsequent radiotherapy was twice as high in the control arm as in the intervention arm, without any specific enquiry about the line of therapy here or for surgical intervention. Information on the first subsequent therapy is available for systemic therapies. In relation to patients with subsequent therapy, approximately the same proportion of patients in both arms received subsequent systemic therapy (81.8% in the intervention arm and 83.7% in the comparator arm). Of the immunotherapies in the control arm, pembrolizumab was the most frequently used drug in the first subsequent systemic therapy (44.4%). In the intervention arm, pembrolizumab was only used in one of 18 patients (5.6%) with first subsequent systemic therapy. The proportion of targeted therapies with first subsequent systemic therapy was higher in the intervention arm than in the control arm (33.3% versus 19.4%). The proportion of chemotherapies with first subsequent systemic therapy was higher in the intervention arm (88.9%) than in the control arm (58.3%). Some of the subsequent systemic therapies administered (e.g. toripalimab, lobaplatin and nedaplatin) are not approved in Germany. The company did not provide any information on whether the drugs were used as monotherapy or as combination therapy.

According to the recommendations of the German Society for Haematology and Medical Oncology (DGHO) [6] for non-small cell lung cancer (NSCLC), the treatment indication is based on the patient's general condition, pretreatment, symptoms, specific comorbidity and preference. The choice of substances is determined by the histological classification of the tumour, molecular pathological alterations (molecular-stratified therapy) and the degree of PD-L1 expression on the tumour cells and on immune cells. Programmed cell death protein 1 (PD-1) or PD-L1 antibodies, such as pembrolizumab and atezolizumab, are recommended as monotherapy for patients with PD-L1 expression ≥ 50% or as combination therapy with chemotherapy for patients irrespective of PD-L1 status [5,6]. The molecularly stratified therapies mentioned in the guideline [6] includes osimertinib and other immunochemotherapies, for example.

A comparison with the guideline recommendations is not possible because no information is available on the use of the drugs as monotherapy or combination therapy, and because it is also unclear how high the proportion of patients with PD-L1 expression ≥-50% is for whom subsequent therapy was generally indicated. Irrespective of this, it is unclear why a high proportion (37.1%) of patients eligible for subsequent therapy, particularly in the intervention arm, ultimately did not receive any subsequent therapy. Overall, it is therefore not possible to assess whether the patients in both treatment arms received guideline-compliant subsequent therapy.

Risk of bias across outcomes (study level)

Table 6 shows the risk of bias across outcomes (risk of bias at study level).

Table 6: Risk of bias across outcomes (study level) – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CheckMate 816	Yes	Yes	No	No	Yes	Yes	Low

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.

b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.

RCT: randomized controlled trial

The risk of bias across outcomes is rated as low for the CheckMate 816 study.

Transferability of the study results to the German health care context

In the company's opinion, the results of the CheckMate 816 study are transferable to the German health care context. It justified this assessment with the fact that the study was also conducted in Western industrialized countries (Europe and North America) with similar population groups (about 44% of the randomized patients in both relevant treatment arms) and about 47% belonged to the "white" ethnic group.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.1.2 Results

2.1.2.1 Presented outcomes

This addendum presents the following patient-relevant outcomes for the PD-L1-positive population of the CheckMate 816 study:

- Mortality
  - overall survival
- Morbidity
  - failure of the curative approach
  - health status, recorded with the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
- Side effects
  - serious adverse events (SAEs)
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-mediated SAEs
  - immune-mediated severe AEs
  - further specific AEs, if any

Table 7 shows the outcomes for which data were available in the CheckMate 816 study (PD-L1-positive population).

Table 7: Matrix of outcomes – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population)

Study	Outcomes										
	Overall survival	Failure of the curative approach[c]	Health status (EQ-5D VAS)	Health-related quality of life	SAEs[d]	Severe AEs[d, e]	Discontinuation due to AEs[f]	Immune-mediated SAEs[g]	Immune-mediated severe AEs[e, g]	Blood and lymphatic system disorders (SOC, severe AEs[e])	Metabolism and nutrition disorders (SOC, severe AEs[e])
CheckMate 816	Yes	Yes	Yes	No[h]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Analysed via time to event (event-free survival, HR) and occurrence of event (RR); includes the following events: disease progression, AE or any other event that precludes surgery; failed R0 resection of the tumour (R1, R2, Rx); recurrence after successful R0 resection; recurrence in patients without surgery; death from any cause.
d. According to the company without events of the PT malignant neoplasm progression and of the PT cancer pain, which are allocated to the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps).
e. Severe AEs are operationalized as CTCAE grade ≥ 3.
f. Operationalized as discontinuation of at least one drug component.
g. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
h. Outcome not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Failure of the curative treatment approach

In the present therapeutic indication, curative therapy is possible in principle. The infeasibility of the planned surgery or recurrence after R0 remission means that the curative treatment approach in this line of therapy has failed. In the present treatment situation, failure of the curative treatment approach in the current line of therapy is a patient-relevant event because, albeit possible in principle, cure is less likely to achieve in a subsequent line of therapy. Failure

of the curative treatment approach is therefore considered a patient-relevant outcome in this assessment.

The statistical analysis plan (SAP) of the CheckMate 816 study defined EFS as time from randomization to any of the following events: progression of disease precluding surgery, progression or recurrence (based on blinded independent central review [BICR], see below) after surgery, or death from any cause.

In addition, the company cited a further operationalization of the EFS outcome in an SAP (AMNOG-SAP) created specifically a priori for the early benefit assessment. According to this, the EFS outcome was operationalized as time from randomization to the first occurrence of any of the following events:

- progression of the disease, AE or any other event precluding surgery
- failed R0 resection of the tumour (R1, R2, Rx)
- recurrence after successful R0 resection
- recurrence in patients without surgery
- death from any cause

Progression of disease was not rated as an event if surgery was still an option.

The first radiographic tumour assessment was to occur 12 weeks (± 7 days) after surgery, or 12 weeks following tumour restaging for patients who did not receive surgery and without tumour progression confirmed by BICR, and then every 12 weeks for 2 years. Subsequent assessments were to occur every 6 months (24 weeks ± 7 days) for 3 years, and then every year (52 weeks ± 7 days) for 5 years or until disease progression or recurrence. The radiographic tumour assessments were sent to a third party for BICR for confirmation of disease progression or recurrence on an on-going basis. Information on the assessment of events by the investigator is not available.

With regard to the first component of the outcome, it should be noted that although the company cited examples of “any other event” such as toxicity, deterioration of health status or refusal of surgery in the AMNOG-SAP, it did not provide any information on the events that had actually occurred in the dossier. It is therefore unclear which events may have been included here at the discretion of the investigator. The proportion of “other events” is 8 (9.0%) versus 11 (12.4%) in the intervention versus control arm and thus accounts for 20% of all EFS events (see Table 9).

With regard to the component of recurrence in patients without surgery, it should be noted that it is unclear how it was to be ensured that patients were disease-free. However, this is ultimately irrelevant, as no such event occurred in any of the patients.

Despite this uncertainty, EFS according to the operationalization per AMNOG-SAP is used as an outcome to represent failure of the curative treatment approach. In addition to the time to occurrence of an event (event-free survival, hazard ratio [HR]), the occurrence of the event (relative risk [RR]) is also relevant for the assessment.

Health status (EQ-5D VAS)

For the outcome on health status (recorded using EQ-5D VAS), the company presented responder analyses for the time to definitive deterioration. In Module 4 W, the company defined definitive deterioration as follows: decrease of the corresponding score by at least the response criterion without subsequent improvement above the response criterion in one of the following recordings. The company's dossier states that the definition likewise applies to all subsequent recordings. For patients for whom no data were available after the first deterioration, the health status was rated as definitely deteriorated, and no censoring was performed.

According to the study protocol, health status was to be recorded until death, end of the study, or withdrawal of consent (see Table 1). The company did not provide any information on the actual observation period for the PD-L1-positive population for this outcome. It is therefore unclear whether it is appropriate to speak of "definitive deterioration" in this situation. In addition, there is a high proportion of patients with "definitive deterioration" for whom there was either no further recording after the first deterioration or for whom there were no subsequent recordings (9 of 24 patients with "definitive deterioration" in the intervention arm [37.5%] versus 5 of 22 patients with "definitive deterioration" in the comparator arm [22.7%]). Hence, there is not a single confirmation of deterioration in these patients. The analysis of the time to first deterioration is therefore used for this addendum. The EQ-5D VAS 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 *General Methods* of the Institute [7].

General notes on side effects outcomes

The company presented time-to-event analyses for all side effects outcomes. Time-to-event analyses are of particular relevance in between-group comparisons with different mean observation periods [7]. However, due to the comparable treatment durations (see Table 3), it is assumed in the present situation that the observation periods between the study arms are also comparable. In the assessment of side effects, the number of patients in whom an

event occurred is primarily relevant. In addition, when analysing the time until occurrence of the event, effects may also result solely from an earlier or later occurrence of the event rather than on the basis of the proportions. For this reason, the relative risk is used in the present assessment.

Discontinuation due to AEs

In line with the company, discontinuation of at least one drug component is used as outcome for the benefit assessment, as any AE leading to discontinuation of any treatment component is relevant.

Immune-mediated AEs

In Appendix 4 G of the dossier, the company provided supplementary analyses on AEs of special interest predefined in the SAP (immune-mediated AEs ["imAEs"], specific AEs ("select AEs") and further AEs of special interest ["AESIs"]). In addition, analyses of severe events (operationalized as CTCAE grade ≥ 3) and serious events are available for these outcomes. In the dossier, the company stated that the AEs of special interest it referred to as immune-mediated AEs, with the exception of endocrine immune-mediated AEs, were events requiring immunomodulatory therapy. This operationalization is unsuitable for fully representing immune-mediated AEs. The outcome of AEs of special interest, which the company referred to as "select AEs", however, constitutes a selection of categories and Preferred Terms (PTs) which are typical immune-mediated AEs and which could require immunosuppressant treatment (e.g. with corticosteroids), but not necessarily so. This operationalization is considered a sufficient approximation of immune-mediated AEs. Both severe AEs (CTCAE grade ≥ 3) and SAEs were considered.

2.1.2.2 Risk of bias

Table 8 describes the risk of bias for the results of the relevant outcomes for the PD-L1-positive population.

Table 8: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population)

Study		Outcomes										
	Study level	Overall survival	Failure of the curative approach[c]	Health status (EQ-5D VAS)	Health-related quality of life	SAEs[d]	Severe AEs[d, e]	Discontinuation due to AEs[f]	Immune-mediated SAEs[g]	Immune-mediated severe AEs[e, g]	Blood and lymphatic system disorders (SOC, severe AEs[e])	Metabolism and nutrition disorders (SOC, severe AEs[e])
CheckMate 816	L	L	L	H[h]	–[i]	L	L	H[h]	L	L	L	L

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Analysed via time to event (event-free survival, HR) and occurrence of event (RR); includes the following events: disease progression, AE or any other event that precludes surgery; failed R0 resection of the tumour (R1, R2, Rx); recurrence after successful R0 resection; recurrence in patients without surgery; death from any cause.
d. According to the company without events of the PT malignant neoplasm progression and of the PT cancer pain, which are allocated to the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps).
e. Severe AEs are operationalized as CTCAE grade ≥ 3.
f. Operationalized as discontinuation of at least one drug component.
g. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
h. Lack of blinding in subjective recording of outcomes or subjective decision to discontinue treatment.
i. Outcome not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; HR: hazard ratio; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

For the PD-L1-positive population, the risk of bias of the results for the outcomes of health status (EQ-5D VAS) and discontinuation due to AEs is rated as high due to the lack of blinding. The risk of bias of the results on overall survival, on failure of the curative approach (both event-free survival [HR] and occurrence of the event [RR]), and on the outcomes in the side

effects category, with the exception of the outcome of discontinuation due to AEs, was rated as low in each case.

2.1.2.3 Results

Table 9 and Table 10 summarize the results of the comparison of nivolumab + platinum-based chemotherapy versus platinum-based chemotherapy for the neoadjuvant treatment of adult patients with resectable NSCLC with tumour cell PD-L1 expression ≥ 1% and high risk of recurrence (PD-L1-positive population) at the data cut-off with database lock on 14 October 2022. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The available Kaplan-Meier curves on outcomes included in the addendum are presented in Appendix A. The company did not present Kaplan-Meier curves for the time-to-event analysis for the EQ-5D VAS (time to first deterioration) with a response threshold of 15 points. Tables on common AEs, SAEs, severe AEs (CTCAE ≥ 3), and discontinuation due to AEs are presented in Appendix B. A list of the categories of immune-mediated AEs, immune-mediated SAEs, and severe immune-mediated AEs (CTCAE grade ≥ 3) in which events occurred is presented as supplementary information in Appendix C.

Table 9: Results (mortality, morbidity) – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population) (multipage table)

Study Outcome category Outcome	Nivolumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[b]		Nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b]
	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[c]
CheckMate 816 (data cut-off with database lock on 14 October 2022)					
Mortality					
Overall survival	89	NA 13 (14.6)	89	NA [45.08; NC] 31 (34.8)	0.37 [0.19; 0.71]; 0.002
Morbidity					
Failure of the curative approach[d]	89	NA [26.55; NC] 37 (41.6)	89	9.05 [4.80; 16.95] 58 (65.2)	0.50 [0.33; 0.75]; 0.001 RR [95% CI]; p-value[e] 0.64 [0.48; 0.85]; 0.002
Progression of disease precluding surgery	89	ND 5 (5.6)	89	ND 8 (9.0)	ND
Locoregional progression	89	ND 4 (4.5)	89	ND 6 (6.7)	ND
Locoregional progression and distant metastasis	89	ND 1 (1.1)	89	ND 0 (0)	ND
Not reported	89	ND 0 (0)	89	ND 2 (2.2)	ND
AE precluding surgery	89	ND 1 (1.1)	89	ND 1 (1.1)	ND
Other events precluding surgery	89	ND 8 (9.0)	89	ND 11 (12.4)	ND
Failed R0 resection of the tumour (R1, R2, Rx)	89	ND 7 (7.9)	89	ND 12 (13.5)	ND
Recurrence after successful R0 resection	89	ND 14 (15.7)	89	ND 21 (23.6)	ND
Locoregional recurrence	89	ND 8 (9.0)	89	ND 11 (12.4)	ND
Distant metastasis	89	ND 6 (6.7)	89	ND 10 (11.2)	ND

Table 9: Results (mortality, morbidity) – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population) (multipage table)

Study **Outcome category** **Outcome**	**Nivolumab + platinum-based chemotherapy[a]**		**Platinum-based chemotherapy[b]**		**Nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b]**
	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[c]**
Recurrence in patients without surgery	89	ND 0 (0)	89	ND 0 (0)	ND
Death from any cause	89	ND 2 (2.2)	89	ND 5 (5.6)	ND
Health status (EQ-5D VAS – time to first deterioration)[f]	84	34.43 [11.86; 46.95] 44 (52.4)	86	23.46 [16.36; NC] 44 (51.2)	0.82 [0.53; 1.25]; 0.350
Health-related quality of life	Outcome not recorded				

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by disease stage at baseline (IB/II vs. IIIA) and sex (male vs. female) according to IRT; for the health status outcome (EQ-5D VAS): model with additional adjustment for baseline value.
d. Includes the following events: disease progression, AE or any other event that precludes surgery; failed R0 resection of the tumour (R1, R2, Rx); recurrence after successful R0 resection; recurrence in patients without surgery; death from any cause.
e. Institute's calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [8]).
f. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).

AE: adverse event; CI: confidence interval; CSR: convexity, symmetry, z-score; CSZ: convex, symmetry, z-score; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; VAS: visual analogue scale

Table 10: Results (side effects) – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (PD-L1-positive population)

Study Outcome category Outcome	Nivolumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[b]		Nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b]
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[c]
CheckMate 816 (data cut-off with database lock on 14 October 2022)					
Side effects					
AEs (supplementary information)	88	85 (96.6)	89	88 (98.9)	–
SAEs[d]	88	25 (28.4)	89	21 (23.6)	1.20 [0.73; 1.98]; 0.532
Severe AEs[d, e]	88	39 (44.3)	89	60 (67.4)	0.66 [0.50; 0.87]; 0.002
Discontinuation due to AEs[f]	88	11 (12.5)	89	14 (15.7)	0.79 [0.38; 1.65]; 0.573
Immune-mediated AEs (supplementary information)	88	49 (55.7)	89	44 (49.4)	–
Immune-mediated SAEs	88	7 (8.0)	89	3 (3.4)	2.36 [0.63; 8.83]; 0.244
Immune-mediated severe AEs[e]	88	9 (10.2)	89	5 (5.6)	1.82 [0.64; 5.22]; 0.283
Blood and lymphatic system disorders (SOC, severe AEs)[e]	88	11 (12.5)	89	27 (30.3)	0.41 [0.22; 0.78]; 0.004
Metabolism and nutrition disorders (SOC, severe AEs)[e]	88	2 (2.3)	89	9 (10.1)	0.22 [0.05; 1.01]; 0.035[g]

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [8]).
d. According to the company without events of the PT malignant neoplasm progression and of the PT cancer pain, which are allocated to the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps).
e. Operationalized as CTCAE grade ≥ 3.
f. Operationalized as discontinuation of at least one drug component.
g. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for the PD-L1-positive population.

Morbidity

Failure of the curative approach

Operationalization

For the present benefit assessment, the outcome of failure of the curative approach is presented via the time to event (HR) and the occurrence of the event (RR). The following events are included in each case: disease progression, AE or any other event that precludes surgery; failed R0 resection of the tumour (R1, R2, Rx); recurrence after successful R0 resection; recurrence in patients without surgery; death from any cause.

Result

For the outcome of failure of the curative approach, a statistically significant difference for time to event (HR) and occurrence of the event (RR) was found in favour of nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for the PD-L1-positive population.

Health status (EQ-5D VAS)

For the outcome of health status (EQ-5D VAS, time to first deterioration), no statistically significant difference between treatment groups was found for the PD-L1-positive population. There are no advantages or disadvantages of nivolumab + platinum-based chemotherapy compared with platinum-based chemotherapy.

Health-related quality of life

Health-related quality of life was not recorded in the CheckMate 816 study.

Side effects

SAEs, discontinuation due to AEs (discontinuation of at least one drug component), immune-mediated SAEs and immune-mediated severe AEs

For the PD-L1-positive population, no statistically significant difference between treatment groups was found for the outcomes of SAEs, discontinuation due to AEs, immune-mediated SAEs or immune-mediated severe AEs. There are no advantages or disadvantages of nivolumab + platinum-based chemotherapy compared with platinum-based chemotherapy.

Severe AEs, blood and lymphatic system disorders (severe AEs), metabolism and nutrition disorders (severe AEs)

For each of the outcomes of severe AEs and the specific AEs of blood and lymphatic system disorders (severe AEs) and metabolism and nutrition disorders (severe AEs), a statistically significant difference in favour of nivolumab + platinum-based chemotherapy versus platinum-based chemotherapy was shown for the PD-L1-positive population.

2.1.2.4 Subgroups and other effect modifiers

The following potential effect modifiers for the PD-L1-positive population were considered for the present addendum:

- age (< 65 years versus ≥ 65 years)
- sex according to case report form (CRF) (female versus male)
- disease stage according to CRF (stage IB/II versus stage IIIA)

The selected characteristics were defined a priori. In the CheckMate 816 study, subgroup analyses were predefined for overall survival and failure of the curative approach. For the outcomes of overall survival and failure of the curative approach (HR), SAEs, severe AEs and discontinuation due to AEs, subgroup analyses are available for the selected characteristics. No subgroup analyses are available for the outcome of EQ-5D VAS (time to first deterioration), immune-mediated SAEs or immune-mediated severe AEs.

For the outcomes of failure of the curative approach (RR), SAEs, severe AEs, discontinuation due to AEs, and the specific AEs of blood and lymphatic system disorders (severe AEs) and metabolism and nutrition disorders (severe AEs), the RR is used as the effect measure in the present data situation, so that separate tests for interaction (Q test) were performed for the subgroup analyses.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 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 presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup analyses do not reveal any effect modifications. Overall, Kaplan-Meier curves for the subgroups are missing for the outcomes analysed via time to the event.

2.1.3 Summary of the results

Overall, at the data cut-off with database lock on 14 October 2022, advantages of nivolumab + platinum-based chemotherapy over platinum-based chemotherapy were shown for the following outcomes:

- overall survival
- failure of the curative approach
- severe AEs
- blood and lymphatic system disorders (severe AEs)
- metabolism and nutrition disorders (severe AEs)

Disadvantages were not observed. Health-related quality of life outcomes were not recorded in the CheckMate 816 study.

2.2 Patients with tumour cell PD-L1 expression ≥-1% and treatment with cisplatin at the start of the study (cisplatin population)

2.2.1 Study characteristics

A detailed characterization of the CheckMate 816 study can be found in dossier assessment A23-74 [1] and its Appendix B.

Planned duration of follow-up observation

Information on the planned duration of the follow-up observation in the CheckMate 816 study can be found in Table 1 and Section 2.1.1.

Characteristics of the cisplatin population

In the CheckMate 816 study, the company presented analyses on 2 patient populations whose neoadjuvant chemotherapy included cisplatin as a platinum component. One population comprises patients who received only cisplatin as the platinum component during the course of the study. The other population comprises patients who started neoadjuvant chemotherapy with cisplatin and were possibly switched to carboplatin during the course of the study because cisplatin therapy was no longer suitable for them. These were 5 patients in the intervention arm and 4 patients in the comparator arm. This addendum looks at the latter population. Table 11 shows the characteristics of the cisplatin population in the CheckMate 816 study.

Table 11: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (cisplatin population) (multipage table)

Study Characteristic Category	Nivolumab + platinum-based chemotherapy[a] N = 66	Platinum-based chemotherapy[b] N = 70
CheckMate 816		
Age [years], mean (SD)	64 (7)	63 (9)
Sex [F/M], %	27/73	27/73
ECOG Performance Status, n (%)		
0	50 (76)	52 (74)
1	16 (24)	18 (26)
> 1	0 (0)	0 (0)
Family origin, n (%)		
White	32 (48[c])	28 (40)
African American	0 (0)	0 (0)
Asian	34 (52)	42 (60)
Region, n (%)		
North America	13 (20)	13 (19)
Europe	15 (23)	10 (14)
Asia	34 (52)	42 (60)
Rest of the world	4 (6)	5 (7)
Smoking status, n (%)		
Never smoker	7 (11)	7 (10)
Smoker (current, former)	59 (89)	62 (89)
Unknown	0 (0)	1 (1)
Disease stage[d] at baseline according to CRF, n (%)		
Stage IB	5 (8)	1 (1)
Stage IIA	10 (15)	17 (24)
Stage IIB	9 (14)	6 (9)
Stage IIIA	42 (64)	45 (64)
Stage IV	0 (0)	1 (1)
PD-L1 status, n (%)		
1–49%	38 (58)	39 (56)
≥ 50%	28 (42)	31 (44)
Tumour histology, n (%)		
Squamous cell carcinoma	30 (45[c])	36 (51)
Non-squamous cell carcinoma	36 (55)	34 (49)

Table 11: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (cisplatin population) (multipage table)

Study Characteristic Category	Nivolumab + platinum-based chemotherapy[a] N = 66	Platinum-based chemotherapy[b] N = 70
Type of platinum component, n (%[c])		
Cisplatin	61 (92[c])	66 (94[c])
Switch from cisplatin to carboplatin	5 (8[c])	4 (6[c])
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)[e]	ND	ND

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented. It is unclear whether it was also possible to switch the chemotherapy component (to paclitaxel) when switching to carboplatin.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented. It is unclear whether it was also possible to switch the chemotherapy component (to paclitaxel) when switching to carboplatin.
c. Institute's calculation.
d. Staging according to IASLC, 7th edition [4].
e. No data are available for the cisplatin population; in the PD-L1-positive population, 18% of patients in the intervention arm and 44% in the control arm discontinued the study (see Table 2)

CRF: case report form; ECOG: Eastern Cooperative Oncology Group; F: female; IASLC: International Association for the Study of Lung Cancer; M: male; n: number of patients in the category; N: number of randomized patients in the relevant population; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

The cisplatin population is a subpopulation of the PD-L1-positive population (proportion in the intervention versus control arm: 74.2% versus 78.7%) and includes patients with a PD-L1 expression of the tumour cells ≥ 1% and treatment with cisplatin at the start of the study. Both treatment arms are largely similar in terms of the demographic and clinical characteristics of the cisplatin population in the CheckMate 816 study. The patients' mean age at study entry was 64 and 63 years, about 3 quarters of patients were male, and slightly less than half (48% versus 40%) were of white family origin. 76% and 74% of patients had an ECOG Performance Status of 0, and the largest proportion of patients (64%) were in stage IIIA disease according to the 7th edition of the IASLC staging criteria [4]. Patients in stage IB are not covered by the approval or the present research question. However, at 8% and 1% of patients respectively, this only affects a small proportion of the cisplatin population.

There is no information on treatment and study discontinuations for the cisplatin population.

Information on the course of the study

Table 12 shows the median and mean treatment duration of the cisplatin population and the median and mean observation period for the outcome of overall survival as well as the outcome categories of morbidity and side effects.

Table 12: Information on the course of the study – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (cisplatin population)

Study **Duration of the study phase** **Outcome category/outcome**	**Nivolumab + platinum-based chemotherapy[a]** **N = 66**	**Platinum-based chemotherapy[b]** **N = 70**
CheckMate 816		
Treatment duration[c] [months[d]]		
Median [min; max]	3.0 [1.4; 15.2]	4.0 [0.1; 14.7]
Mean (SD)	3.7 (2.3)	4.3 (2.4)
Observation period [months[d]]		
Overall survival		
Median [min; max][e]	42.1 [2.7; 57.5]	40.1 [1.4; 53.9]
Mean (SD)[e]	39.5 (12.7)	33.7 (15.4)
Morbidity	ND	ND
Side effects	ND	ND

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented. It is unclear whether it was also possible to switch the chemotherapy component (to paclitaxel) when switching to carboplatin.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented. It is unclear whether it was also possible to switch the chemotherapy component (to paclitaxel) when switching to carboplatin.
c. Includes neoadjuvant and optional adjuvant study treatment.
d. Institute's calculation from weeks to months.
e. The observation period was presumably determined as the time from randomization until death or until the last data cut-off with database lock in October 2022.

max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

In contrast to the PD-L1-positive population, a difference in treatment duration between the treatment arms was shown in the cisplatin population (intervention versus control: mean of 3.7 months versus 4.3 months, median of 3.0 months versus 4.0 months).

Data on the observation period are only available for the cisplatin population for the outcome of overall survival. The mean observation period for overall survival was 39.5 months in the intervention arm and 33.7 months in the control arm.

Information on adjuvant therapy and subsequent therapies

For the cisplatin population, there is no information on adjuvant therapy or on subsequent therapies administered.

Risk of bias across outcomes (study level)

The risk of bias across outcomes is rated as low for the CheckMate 816 study. More detailed information can be found in Table 8 in Section 2.1.1.

Transferability of the study results to the German health care context

The company provided no information on the transferability of the study results of the cisplatin population to the German health care context.

2.2.2 Results

2.2.2.1 Presented outcomes

This addendum presents the following patient-relevant outcomes for the cisplatin population of the CheckMate 816 study:

- Mortality
  - overall survival
- Morbidity
  - failure of the curative approach
  - health status, recorded with the EQ-5D VAS
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-mediated SAEs
  - immune-mediated severe AEs
  - further specific AEs, if any

Table 13 shows the outcomes for which data were available in the CheckMate 816 study (cisplatin population).

Table 13: Matrix of outcomes – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (cisplatin population)

Study	Outcomes									
	Overall survival	Failure of the curative approach[c]	Health status (EQ-5D VAS)	Health-related quality of life	SAEs[d]	Severe AEs[d, e]	Discontinuation due to AEs[f]	Immune-mediated SAEs[g]	Immune-mediated severe AEs[e, g]	Other specific AEs
CheckMate 816	Yes	Yes	No[h]	No[i]	Yes	Yes	Yes	No[j]	No[j]	No[k]

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented. It is unclear whether it was also possible to switch the chemotherapy component (to paclitaxel) when switching to carboplatin.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented. It is unclear whether it was also possible to switch the chemotherapy component (to paclitaxel) when switching to carboplatin.
c. Analysed via time to event (event-free survival, HR) and occurrence of event (RR); includes the following events: disease progression, AE or any other event that precludes surgery; failed R0 resection of the tumour (R1, R2, Rx); recurrence after successful R0 resection; recurrence in patients without surgery; death from any cause.
d. According to the company without events of the PT malignant neoplasm progression and of the PT cancer pain, which are allocated to the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps).
e. Severe AEs are operationalized as CTCAE grade ≥ 3.
f. Operationalized as discontinuation of at least one drug component.
g. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
h. No suitable data; see section below.
i. Outcome not recorded.
j. Analyses on immune-mediated SAEs and severe AEs are not available.
k. Analyses on AEs are not available, a choice of specific AEs is therefore not possible.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Notes on the outcomes of failure of the curative treatment approach, discontinuation due to AEs, and immune-mediated AEs can be found in Section 2.1.2.1.

Health status (EQ-5D VAS)

For the cisplatin population, the company only presented an analysis of the time to definitive deterioration. However, this analysis is not suitable for the assessment in the present data situation because no information is available on the proportion of patients with "definitive deterioration" for whom either no more recordings were conducted after the first deterioration or for whom subsequent recordings were missing, and because the proportion of these patients was high in the PD-L1-positive population (for detailed reasons, see Section 2.1.2.1). In addition, information on the observation period is missing. The company did not present the analysis required in the present data situation (time to first deterioration) for the cisplatin population.

General notes on side effects outcomes

The company presented time-to-event analyses for all side effects outcomes. Time-to-event analyses are of particular relevance in between-group comparisons with different mean observation periods [7]. In contrast to the PD-L1-positive population, for the cisplatin population, the difference in treatment duration between the treatment arms (intervention versus control: mean of 3.7 months versus 4.3 months, median of 3.0 months versus 4.0 months, see Table 12) and the resulting difference in the duration of follow-up observation for outcomes in the side effects category is rated as so large that time-to-event analyses are presented in the present data situation. Data on the actual observation periods of these outcomes are not available.

2.2.2.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes of the cisplatin population.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (cisplatin population)

Study	Study level	Outcomes									
		Overall survival	Failure of the curative approach[c]	Health status (EQ-5D VAS)	Health-related quality of life	SAEs[d]	Severe AEs[d, e]	Discontinuation due to AEs[f]	Immune-mediated SAEs[g]	Immune-mediated severe AEs[e, g]	Other specific AEs
CheckMate 816	L	L	L	–[h]	–[i]	H[j]	H[j]	H[k]	–[l]	–[l]	–[m]

a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented. It is unclear whether it was also possible to switch the chemotherapy component (to paclitaxel) when switching to carboplatin.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented. It is unclear whether it was also possible to switch the chemotherapy component (to paclitaxel) when switching to carboplatin.
c. Analysed via time to event (event-free survival, HR) and occurrence of event (RR); includes the following events: disease progression, AE or any other event that precludes surgery; failed R0 resection of the tumour (R1, R2, Rx); recurrence after successful R0 resection; recurrence in patients without surgery; death from any cause.
d. According to the company without events of the PT malignant neoplasm progression and of the PT cancer pain, which are allocated to the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps).
e. Severe AEs are operationalized as CTCAE grade ≥ 3.
f. Operationalized as discontinuation of at least one drug component.
g. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
h. No suitable data; see Section 2.2.2.1.
i. Outcome not recorded.
j. Incomplete observation for potentially informative reasons; see next section.
k. Lack of blinding in subjective decision for discontinuation.
l. Analyses on immune-mediated SAEs and severe AEs are not available.
m. Analyses on AEs are not available, a choice of specific AEs is therefore not possible.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; HR: hazard ratio; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results for the outcomes of overall survival and failure of the curative approach (both event-free survival [HR] and occurrence of the event [RR]) is assessed as low in each case.

In contrast to the PD-L1-positive population, in the cisplatin population, the difference in treatment duration between the treatment arms (intervention versus control: mean of 3.7 months versus 4.3 months, median of 3.0 months versus 4.0 months) and the resulting difference in the duration of follow-up observation for outcomes in the side effects category is rated as relevant: Follow-up observation of AEs was planned up to 100 days after the last dose of neoadjuvant treatment, up to 90 days after surgery, or up to 30 days after the last dose of optional adjuvant treatment, whichever was the longest. Decisions as to whether surgery or subsequent adjuvant treatment should follow neoadjuvant treatment and how long the respective treatment phase would last were made on a patient-specific basis at the discretion of the investigator. Follow-up observation was therefore driven by the reasons for treatment decisions. It can be assumed that the reasons differed between the arms, as the treatment decisions differed. Due to a possible association between the reason for longer or shorter treatment duration and the outcomes of SAEs and severe AEs, there were therefore incomplete observations for potentially informative reasons. Thus, the risk of bias for the results on the outcomes of SAEs and severe AEs was rated as high.

The risk of bias in the outcome of discontinuation due to AEs was rated as high because of lack of blinding in the presence of subjective decision on discontinuation.

No analyses are available for the outcomes of immune-mediated SAEs and immune-mediated severe AEs for the cisplatin population.

2.2.2.3 Results

Table 15 summarizes the results of the comparison of nivolumab + platinum-based chemotherapy versus platinum-based chemotherapy for the neoadjuvant treatment of adult patients with resectable NSCLC with tumour cell PD-L1 expression ≥ 1%, treatment with cisplatin at the start of the study and high risk of recurrence (cisplatin population) at the data cut-off with database lock on 14 October 2022. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

For the cisplatin population, neither Kaplan-Meier curves for the time-to-event analyses of the outcomes nor results on common AEs are available. Furthermore, there is no list of the categories of immune-mediated AEs, immune-mediated SAEs and severe immune-mediated AEs (CTCAE grade ≥ 3) in which events occurred.

Table 15: Results (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (cisplatin population) (multipage table)

Study **Outcome category** **Outcome**	**Nivolumab + platinum-based chemotherapy[a]**		**Platinum-based chemotherapy[b]**		**Nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b]**
	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[c]**
CheckMate 816 (data cut-off with database lock on 14 October 2022)					
Mortality					
Overall survival	66	NA 9 (13.6)	70	NA 23 (32.9)	0.37 [0.17; 0.79]; 0.008
Morbidity					
Failure of the curative approach[d]	66	NA [19.38; NC] 27 (40.9)	70	14.75 [5.29; 24.94] 43 (61.4)	0.54 [0.34; 0.88]; 0.012 RR [95% CI]; p-value[e] 0.67 [0.47; 0.94]; 0.018
Progression of disease precluding surgery				ND	
AE precluding surgery				ND	
Other events precluding surgery				ND	
Failed R0 resection of the tumour (R1, R2, Rx)				ND	
Recurrence after successful R0 resection				ND	
Recurrence in patients without surgery				ND	
Death from any cause				ND	
Health status (EQ-5D VAS – time to first deterioration)[f]				ND	

Table 15: Results (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (cisplatin population) (multipage table)

Study **Outcome category** **Outcome**	**Nivolumab + platinum-based chemotherapy[a]**		**Platinum-based chemotherapy[b]**		**Nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b]**
	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[c]**
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)	66	0.10 [0.07; 0.16] 63 (95.5)	70	0.10 [0.07; 0.13] 70 (100)	–
SAEs[g]	66	NA 20 (30.3)	70	NA 17 (24.3)	1.26 [0.66, 2.41; 0.476
Severe AEs[g, h]	66	NA [3.19; NC] 27 (40.9)	70	2.60 [1.61; 3.58] 45 (64.3)	0.57 [0.35; 0.91]; 0.018
Discontinuation due to AEs[i]	66	NA 10 (15.2)	70	NA 10 (14.3)	1.06 [0.44; 2.56]; 0.890
Immune-mediated AEs (supplementary information)	66	2.79 [0.49; NC] 34 (51.5)	70	NA [2.56; NC] 30 (42.9)	–
Immune-mediated SAEs				ND	
Immune-mediated severe AEs[g]				ND	

Table 15: Results (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b] (cisplatin population) (multipage table)

Study Outcome category Outcome	Nivolumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[b]		Nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[b]
	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[c]
a. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not suitable and the reason for this was documented. It is unclear whether it was also possible to switch the chemotherapy component (to paclitaxel) when switching to carboplatin. b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not suitable and the reason for this was documented. It is unclear whether it was also possible to switch the chemotherapy component (to paclitaxel) when switching to carboplatin. c. HR and CI: Cox proportional hazards model, p-value: log-rank test; unstratified in each case; for the health status outcome (EQ-5D VAS): model with additional adjustment for baseline value. d. Includes the following events: disease progression, AE or any other event that precludes surgery; failed R0 resection of the tumour (R1, R2, Rx); recurrence after successful R0 resection; recurrence in patients without surgery; death from any cause. e. Institute's calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [8]). f. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100). g. According to the company without events of the PT malignant neoplasm progression and of the PT cancer pain, which are allocated to the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps). h. Operationalized as CTCAE grade ≥ 3. i. Operationalized as discontinuation of at least one drug component. AE: adverse event; 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; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale				

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for the cisplatin population.

Morbidity

Failure of the curative approach

Operationalization

For the present benefit assessment, the outcome of failure of the curative approach is presented via the time to event (HR) and the occurrence of the event (RR). The following events are included in each case: disease progression, AE or any other event that precludes surgery; failed R0 resection of the tumour (R1, R2, Rx); recurrence after successful R0 resection; recurrence in patients without surgery; death from any cause.

Result

For the outcome of failure of the curative approach, a statistically significant difference for time to event (HR) and occurrence of the event (RR) was found in favour of nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for the cisplatin population.

Health status (EQ-5D VAS)

No data are available for the cisplatin population for health status (recorded using EQ-5D VAS, time to first deterioration) (for reasons, see Section 2.2.2.1).

Health-related quality of life

Health-related quality of life was not recorded in the CheckMate 816 study.

Side effects

SAEs, discontinuation due to AEs (discontinuation of at least one drug component)

For the cisplatin population, no statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. There are no advantages or disadvantages of nivolumab + platinum-based chemotherapy compared with platinum-based chemotherapy.

Severe AEs

For the outcome of severe AEs, a statistically significant difference was found in favour of nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for the cisplatin population.

Immune-mediated SAEs and immune-mediated severe AEs

No data are available for immune-mediated SAEs or immune-mediated severe AEs for the cisplatin population.

2.2.2.4 Subgroups and other effect modifiers

No subgroup analyses are available for the cisplatin population.

2.2.3 Summary of the results

For the cisplatin population, at the data cut-off with database lock on 14 October 2022, advantages of nivolumab + platinum-based chemotherapy over platinum-based chemotherapy were overall shown for the following outcomes:

- overall survival
- failure of the curative approach
- severe AEs

Disadvantages were not observed. Health-related quality of life outcomes were not recorded in the CheckMate 816 study.

In comparison with the PD-L1-positive population (see Section 2.1), there are greater uncertainties in categorizing the results of the cisplatin population due to a lack of data.

2.3 Summary

The conclusion on the added benefit of nivolumab + platinum-based chemotherapy compared with the ACT specified by the G-BA does not change in comparison with dossier assessment A23-74 [1].

The following Table 16 shows the result of the benefit assessment of nivolumab, taking into account dossier assessment A23-74 and the present addendum.

Table 16: Nivolumab + platinum-based chemotherapy – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Neoadjuvant treatment of resectable NSCLC with PD-L1 expression in ≥ 1% of tumour cells in adults at high risk of recurrence	Individualized treatment[b] selected from: ▪ Neoadjuvant systemic chemotherapy selected from ▫ cisplatin in combination with vinorelbine and ▫ cisplatin in combination with paclitaxel (only for patients in the advanced stage) and ▪ simultaneous radiochemotherapy with cisplatin in combination with vinorelbine as chemotherapy taking into account tumour stage, presence/absence of Pancoast tumour, and feasibility of R0 resection	Added benefit not proven

a. Presented is the ACT specified by the G-BA. The available guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association as per § 35a (7) sentence 4 SGB V discuss both approved and unapproved drug therapies for the neoadjuvant and adjuvant treatment of resectable NSCLC. According to the BSG comments on the judgement dated 22 February 2023 (reference number: B 3 KR 14/21 R), drugs which are not approved for the present therapeutic indication and whose off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered ACTs in the narrower sense of §2 (1), sentence 3, §12 SGB V.

b. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization).

ACT: appropriate comparator therapy; BSG: Federal Social Court; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; SGB: Social Code Book

The G-BA decides on the added benefit.

3 References

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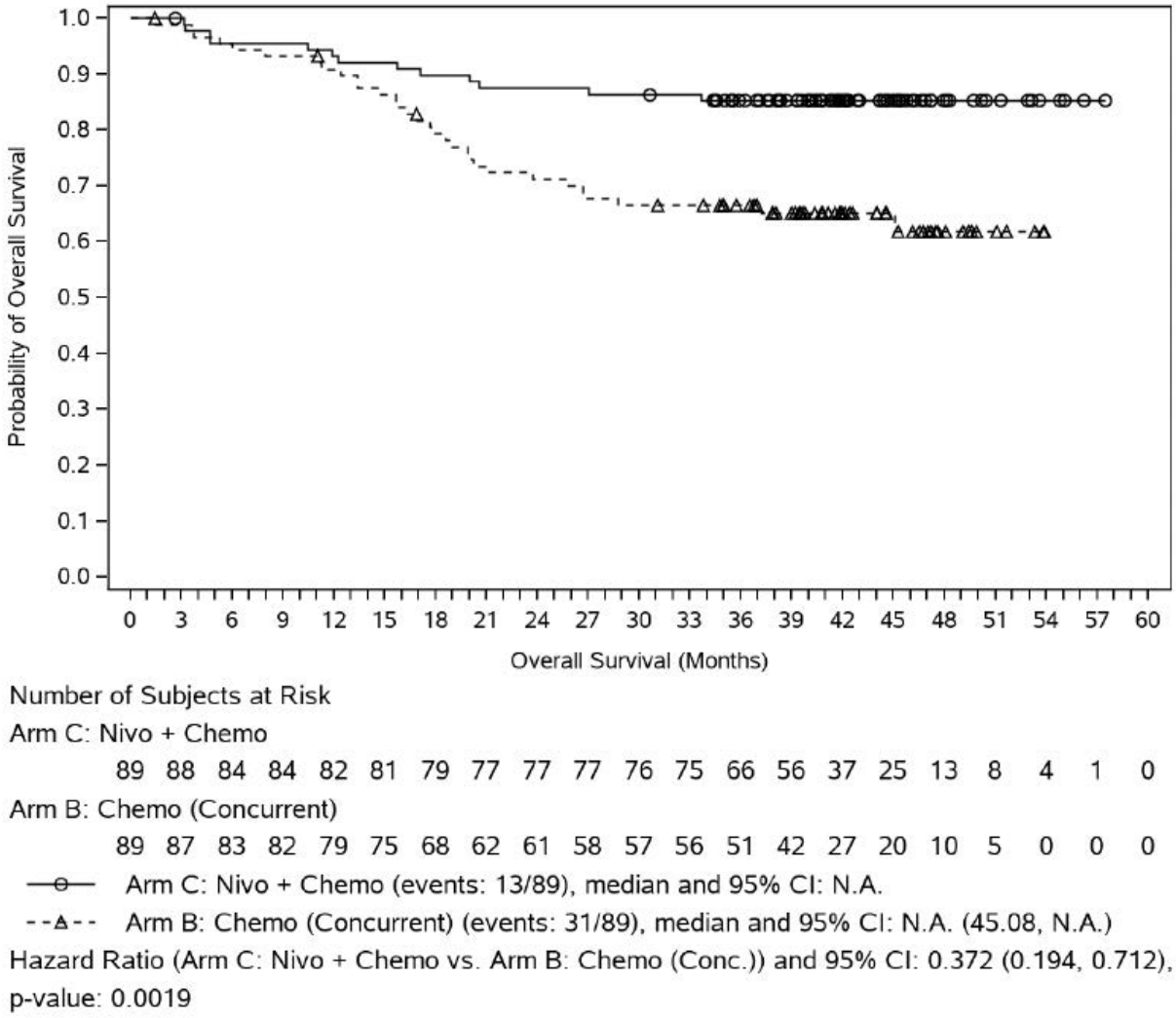
Appendix A Kaplan-Meier curves (PD-L1-positive population)



Number of Subjects at Risk

Arm C: Nivo + Chemo

89 88 84 84 82 81 79 77 77 77 76 75 66 56 37 25 13 8 4 1 0

Arm B: Chemo (Concurrent)

89 87 83 82 79 75 68 62 61 58 57 56 51 42 27 20 10 5 0 0 0

—o— Arm C: Nivo + Chemo (events: 13/89), median and 95% CI: N.A.

--△-- Arm B: Chemo (Concurrent) (events: 31/89), median and 95% CI: N.A. (45.08, N.A.)

Hazard Ratio (Arm C: Nivo + Chemo vs. Arm B: Chemo (Conc.)) and 95% CI: 0.372 (0.194, 0.712), p-value: 0.0019

Figure 1: Kaplan-Meier curves for the outcome of overall survival; (CheckMate 816 study, PD-L1-positive population)

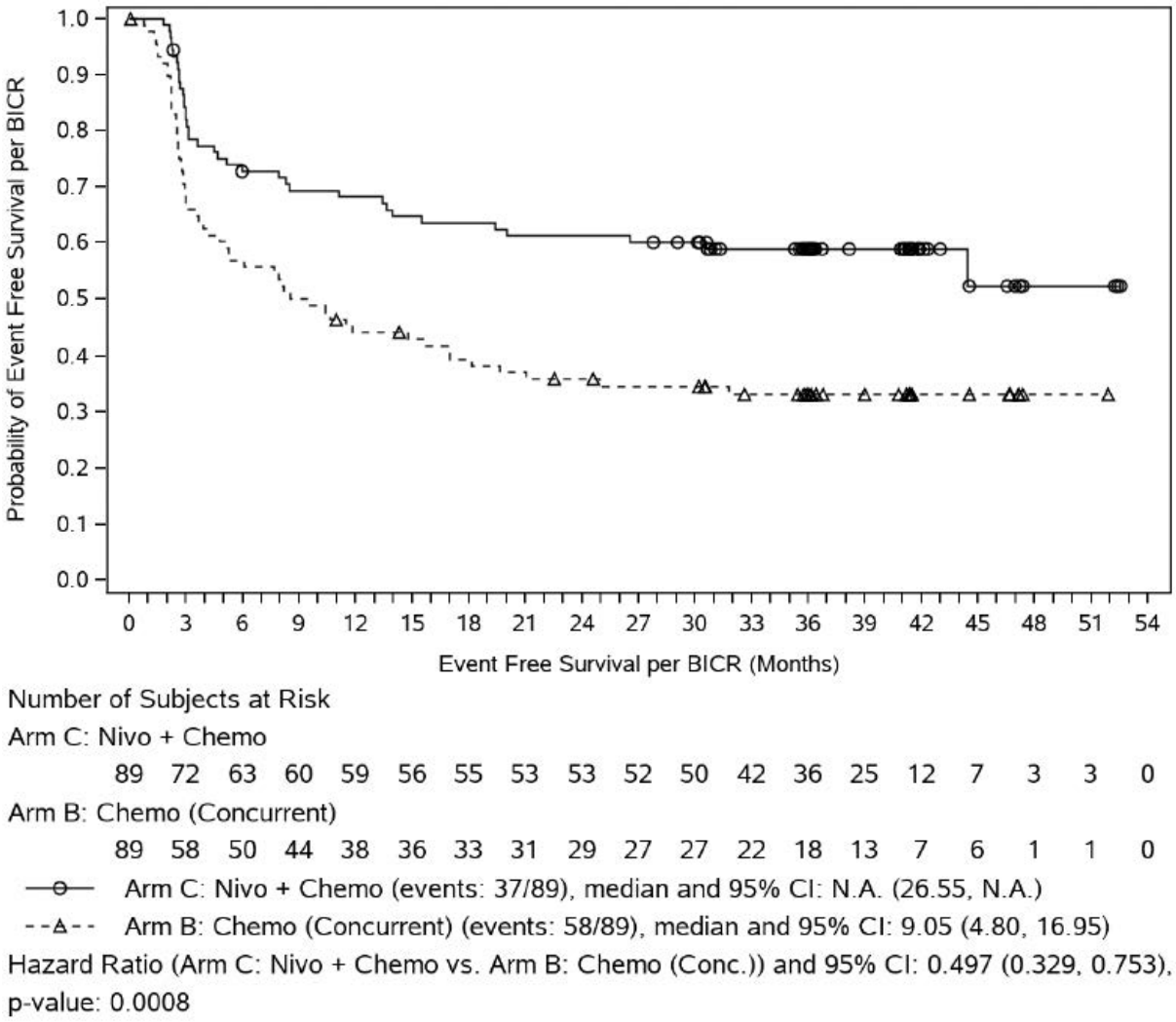


Figure 2: Kaplan-Meier curves for the outcome of failure of the curative approach (CheckMate 816 study, PD-L1-positive population)

Appendix B Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for System Organ Classes (SOCs) and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity): events that occurred in at least 10% of patients in one study arm
- overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- in addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all results (SOCs/PTs) that resulted in discontinuation is provided.

Table 17: Common AEs[a] – RCT, direct comparison: nivolumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[c] (PD-L1-positive population) (multipage table)

Study	Patients with event n (%)	
SOC[d] PT[d]	Nivolumab + platinum-based chemotherapy[b] N = 88	Platinum-based chemotherapy[c] N = 89
CheckMate 816		
Overall AE rate	85 (96.6)	88 (98.9)
Gastrointestinal Disorders	58 (65.9)	62 (69.7)
Nausea	36 (40.9)	42 (47.2)
Constipation	34 (38.6)	31 (34.8)
Vomiting	11 (12.5)	14 (15.7)
Diarrhoea	10 (11.4)	12 (13.5)
General disorders and administration site conditions	54 (61.4)	52 (58.4)
Malaise	14 (15.9)	15 (16.9)
Asthenia	12 (13.6)	8 (9.0)
Fatigue	12 (13.6)	14 (15.7)
Pain	12 (13.6)	16 (18.0)
Pyrexia	12 (13.6)	11 (12.4)
Blood and Lymphatic System Disorders	43 (48.9)	53 (59.6)
Anaemia	36 (40.9)	38 (42.7)
Neutropenia	9 (10.2)	20 (22.5)
Leukopenia	8 (9.1)	10 (11.2)
Investigations	43 (48.9)	45 (50.6)
Neutrophil count decreased	15 (17.0)	23 (25.8)
White blood cell count decreased	10 (11.4)	13 (14.6)
Respiratory, thoracic and mediastinal disorders	43 (48.9)	47 (52.8)
Cough	13 (14.8)	15 (16.9)
Hiccups	11 (12.5)	16 (18.0)
Metabolism and Nutrition disorders	41 (46.6)	42 (47.2)
Decreased appetite	25 (28.4)	25 (28.1)
Skin and subcutaneous tissue disorders	35 (39.8)	30 (33.7)
Rash	12 (13.6)	4 (4.5)
Alopecia	10 (11.4)	16 (18.0)
Injury, poisoning and procedural complications	28 (31.8)	22 (24.7)
Procedural pain	10 (11.4)	4 (4.5)
Infections and infestations	22 (25.0)	17 (19.1)

Table 17: Common AEs[a] – RCT, direct comparison: nivolumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[c] (PD-L1-positive population) (multipage table)

Study	**Patients with event n (%)**	
SOC[d] PT[d]	**Nivolumab + platinum-based chemotherapy[b] N = 88**	**Platinum-based chemotherapy[c] N = 89**
Pneumonia	9 (10.2)	6 (6.7)
Musculoskeletal and connective tissue disorders	22 (25.0)	23 (25.8)
Arthralgia	11 (12.5)	4 (4.5)
Nervous system disorders	22 (25.0)	22 (24.7)
Vascular disorders	14 (15.9)	13 (14.6)
Psychiatric disorders	13 (14.8)	18 (20.2)
Insomnia	7 (8.0)	10 (11.2)
Cardiac disorders	10 (11.4)	14 (15.7)

a. The company provided no information on cut-off values; based on the available frequencies, it is assumed that these are events that occurred in ≥ 10% of patients in at least one study arm.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
d. MedDRA version 25.0; SOC and PT notation taken unmodified from Module 4 W.

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 18: Common SAEs[a] – RCT, direct comparison: nivolumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[c] (PD-L1-positive population)

Study	**Patients with event n (%)**	
SOC[d]	**Nivolumab + platinum-based chemotherapy[b] N = 88**	**Platinum-based chemotherapy[c] N = 89**
CheckMate 816		
Overall SAE rate	25 (28.4)	22 (24.7)
Infections and infestations	7 (8.0)	6 (6.7)
Respiratory, thoracic and mediastinal disorders	5 (5.7)	3 (3.4)
Blood and Lymphatic System Disorders	2 (2.3)	5 (5.6)

a. The company provided no information on cut-off values; based on the available frequencies, it is assumed that these are events that occurred in ≥ 5% of patients in at least one study arm.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
d. MedDRA version 25.0; SOC notation taken unmodified from Module 4 W.

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; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 19: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: nivolumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[c] (PD-L1-positive population)

Study	**Patients with event n (%)**	
SOC[d] PT[d]	**Nivolumab + platinum-based chemotherapy[b] N = 88**	**Platinum-based chemotherapy[c] N = 89**
CheckMate 816		
Overall rate of severe AEs (CTCAE grade ≥ 3)	39 (44.3)	60 (67.4)
Investigations	13 (14.8)	16 (18.0)
Neutrophil count decreased	8 (9.1)	14 (15.7)
Blood and Lymphatic System Disorders	11 (12.5)	27 (30.3)
Neutropenia	6 (6.8)	15 (16.9)
Anaemia	3 (3.4)	9 (10.1)
Leukopenia	1 (1.1)	5 (5.6)
Infections and infestations	8 (9.1)	6 (6.7)
Respiratory, thoracic and mediastinal disorders	3 (3.4)	6 (6.7)
Metabolism and nutrition disorders	2 (2.3)	9 (10.1)

a. The company provided no information on cut-off values; based on the available frequencies, it is assumed that these are events that occurred in ≥ 5% of patients in at least one study arm.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
d. MedDRA version 25.0; SOC and PT notation taken unmodified from Module 4 W.

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

Table 20: Discontinuation due to AEs[a] – RCT, direct comparison: nivolumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[c] (PD-L1-positive population) (multipage table)

Study	**Patients with event n (%)**	
SOC[d] **PT[d]**	**Nivolumab + platinum-based chemotherapy[b]** **N = 88**	**Platinum-based chemotherapy[c]** **N = 89**
CheckMate 816		
Overall rate of discontinuations due to AEs	11 (12.5)	14 (15.7)
Investigations	4 (4.5)	4 (4.5)
Neutrophil count decreased	2 (2.3)	3 (3.4)
Blood creatinine increased	1 (1.1)	1 (1.1)
Platelet count decreased	1 (1.1)	0 (0)
Immune system disorders	3 (3.4)	0 (0)
Anaphylactic reaction	3 (3.4)	0 (0)
Infections and infestations	2 (2.3)	2 (2.2)
Pneumonia	1 (1.1)	0 (0)
Sepsis	1 (1.1)	0 (0)
Enterocolitis infectious	0 (0)	1 (1.1)
Herpes zoster	0 (0)	1 (1.1)
Musculoskeletal and connective tissue disorders	1 (1.1)	0 (0)
Muscular weakness	1 (1.1)	0 (0)
Skin and subcutaneous tissue disorders	1 (1.1)	0 (0)
Rash	1 (1.1)	0 (0)
Blood and lymphatic system disorders	0 (0)	5 (5.6)
Neutropenia	0 (0)	5 (5.6)
General disorders and administration site conditions	0 (0)	1 (1.1)
Asthenia	0 (0)	1 (1.1)
Metabolism and nutrition disorders	0 (0)	1 (1.1)
Decreased appetite	0 (0)	1 (1.1)
Nervous system disorders	0 (0)	2 (2.2)
Neuropathy peripheral	0 (0)	1 (1.1)
Taste disorder	0 (0)	1 (1.1)
Renal and urinary disorders	0 (0)	1 (1.1)
Chronic kidney disease	0 (0)	1 (1.1)

Table 20: Discontinuation due to AEs[a] – RCT, direct comparison: nivolumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[c] (PD-L1-positive population) (multipage table)

Study	Patients with event n (%)	
SOC[d] PT[d]	Nivolumab + platinum-based chemotherapy[b] N = 88	Platinum-based chemotherapy[c] N = 89

a. Therapy was considered discontinued if one or more drugs of a regimen were discontinued.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
d. MedDRA version 25.0; SOC and PT notation taken unmodified from Module 4 W.

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

Appendix C Supplementary presentation of results on categories of immune-mediated AEs, severe immune-mediated AEs (CTCAE grade ≥ 3), and immune-mediated SAEs

Table 21: Categories of immune-mediated AEs[a] – RCT, direct comparison: nivolumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[c] (PD-L1-positive population)

Study	Patients with event n (%)	
Category[d]	**Nivolumab + platinum-based chemotherapy[b] N = 88**	**Platinum-based chemotherapy[c] N = 89**
CheckMate 816		
Overall rate of immune-mediated AEs	49 (55.7)	44 (49.4)
SUBJECTS WITH ENDOCRINE AES	9 (10.2)	1 (1.1)
SUBJECTS WITH GASTROINTESTINAL AES	10 (11.4)	13 (14.6)
SUBJECTS WITH HEPATIC AES	10 (11.4)	14 (15.7)
SUBJECTS WITH PULMONARY AES	2 (2.3)	1 (1.1)
SUBJECTS WITH RENAL AES	10 (11.4)	11 (12.4)
SUBJECTS WITH SKIN AES	26 (29.5)	13 (14.6)
SUBJECTS WITH HYPERSENSITIVITY/INFUSION REACTION AES	7 (8.0)	4 (4.5)

a. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
d. Category notation taken unmodified from Module 4 W.

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

Table 22: Categories of immune-mediated SAEs[a] – RCT, direct comparison: nivolumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[c] (PD-L1-positive population)

Study	**Patients with event n (%)**	
Category[d]	**Nivolumab + platinum-based chemotherapy[b] N = 88**	**Platinum-based chemotherapy[c] N = 89**
CheckMate 816		
Overall rate of immune-mediated SAEs	7 (8.0)	3 (3.4)
SUBJECTS WITH ENDOCRINE AES	2 (2.3)	0 (0)
SUBJECTS WITH GASTROINTESTINAL AES	0 (0)	1 (1.1)
SUBJECTS WITH HEPATIC AES	0 (0)	0 (0)
SUBJECTS WITH PULMONARY AES	1 (1.1)	1 (1.1)
SUBJECTS WITH RENAL AES	2 (2.3)	1 (1.1)
SUBJECTS WITH SKIN AES	1 (1.1)	0 (0)
SUBJECTS WITH HYPERSENSITIVITY/INFUSION REACTION AES	1 (1.1)	0 (0)

a. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
d. Category notation taken unmodified from Module 4 W.

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

Table 23: Categories of immune-mediated severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: nivolumab + platinum-based chemotherapy[b] vs. platinum-based chemotherapy[c] (PD-L1-positive population)

Study	**Patients with event n (%)**	
Category[d]	**Nivolumab + platinum-based chemotherapy[b] N = 88**	**Platinum-based chemotherapy[c] N = 89**
CheckMate 816		
Overall rate of immune-mediated severe AEs (CTCAE grade ≥ 3)	9 (10.2)	5 (5.6)
SUBJECTS WITH ENDOCRINE AES	2 (2.3)	0 (0)
SUBJECTS WITH GASTROINTESTINAL AES	1 (1.1)	1 (1.1)
SUBJECTS WITH HEPATIC AES	1 (1.1)	2 (2.2)
SUBJECTS WITH PULMONARY AES	0 (0)	1 (1.1)
SUBJECTS WITH RENAL AES	1 (1.1)	0 (0)
SUBJECTS WITH SKIN AES	3 (3.4)	0 (0)
SUBJECTS WITH HYPERSENSITIVITY/INFUSION REACTION AES	3 (3.4)	1 (1.1)

a. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
b. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
c. Investigator-choice chemotherapy: cisplatin + gemcitabine (only for squamous histology), or cisplatin + pemetrexed (only for non-squamous histology), or cisplatin + vinorelbine, or cisplatin + docetaxel, or carboplatin + paclitaxel. Carboplatin could be used instead of cisplatin in patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented.
d. Category notation taken unmodified from Module 4 W.

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