Nivolumab
(NSCLC, neoadjuvant)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

I Table of contents

Page

I List of tables I.3
I List of abbreviations I.4
I 1 Executive summary of the benefit assessment I.5
I 2 Research question I.11
I 3 Information retrieval and study pool I.13
I 3.1 Evidence presented by the company – CheckMate 816 study I.13
I 3.2 Assessment of the evidence presented by the company I.15
I 3.2.1 Insufficient implementation of the ACT I.16
I 3.2.2 Effect on overall survival not transferable I.17
I 4 Results on added benefit I.19
I 5 Probability and extent of added benefit I.20
I 6 References for English extract I.21

I List of tables[2]

Page

Table 2: Research question of the benefit assessment of nivolumab in combination with platinum-based chemotherapy I.5
Table 3: Nivolumab + platinum-based chemotherapy – probability and extent of added benefit I.10
Table 4: Research question of the benefit assessment of nivolumab in combination with platinum-based chemotherapy I.11
Table 5: Nivolumab + platinum-based chemotherapy – probability and extent of added benefit I.20

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
EFS	event-free survival
EGFR	epidermal growth factor receptor
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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
pCR	pathological complete response
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nivolumab (in combination with platinum-based chemotherapy). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 28 July 2023.

Research question

The aim of this report is to assess the added benefit of nivolumab in combination with platinum-based chemotherapy (hereinafter referred to as nivolumab + platinum-based chemotherapy) compared with the appropriate comparator therapy (ACT) for the neoadjuvant treatment of resectable non-small cell lung cancer (NSCLC) with tumour cell PD-L1 expression ≥ 1% in adults at high risk of recurrence.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of nivolumab in combination with platinum-based chemotherapy

Therapeutic indication	**ACT**[a]
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
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	

In the context of the specification of the ACT, the G-BA points out that the available guidelines and scientific-medical societies and/or the Drug Commission of the German Medical Association in accordance with § 35a (7), sentence 4 SGB V list both approved and unapproved drugs for the neoadjuvant and adjuvant treatment of resectable NSCLC. According to the BSG comments on the judgement of 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 as ACTs in the narrower sense of § 2 (1), sentence 3, § 12 SGB V.

In agreement with the G-BA, the company initially considered the ACT to be individualized therapy with a choice of neoadjuvant systemic chemotherapy or simultaneous radiochemotherapy, taking into account tumour stage, the presence/absence of a Pancoast tumour, and feasibility of R0 resection. However, when naming individual treatment regimens in the context of neoadjuvant systemic chemotherapy and simultaneous radiochemotherapy, the company deviated from the ACT defined by the G-BA.

The present assessment is implemented in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of any added benefit.

Results

The company identified the RCT CheckMate 816 for the direct comparison of nivolumab + platinum-based chemotherapy versus the ACT. This study is an open-label, multicentre RCT comparing nivolumab + platinum-based chemotherapy versus platinum-based chemotherapy in the neoadjuvant treatment of NSCLC.

The study included adult patients with histologically confirmed and resectable NSCLC of stage IB (tumour size ≥ 4 cm), II, or IIIA, each according to the staging criteria of the International Association for the Study of Lung Cancer (IASLC), 7th edition. Furthermore, patients had to be in good general condition as measured by an Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) of 0 or 1 at baseline. The study excluded patients with known epidermal growth factor receptor (EGFR) mutations or ALK translocation as well as those with previous chemotherapy or other cancer therapy in an early stage of NSCLC. Tumour cell PD-L1 expression had to be determined for patients to be enrolled in the study.

The original study protocol provided for randomization in a 1:1 ratio into the following 2 treatment arms: nivolumab + ipilimumab (arm A) versus platinum-based chemotherapy (arm B). The revised protocol 02 dated 6 July 2017 introduced a 3rd treatment arm (arm C, nivolumab + platinum-based chemotherapy), and randomization was thereafter carried out in

a 1:1:1 ratio. As of protocol revision 03 dated 21 September 2018, no further patients were randomized into to the nivolumab + ipilimumab arm, with randomization then being carried out only into the 2 remaining arms in a 1:1 ratio. The analyses presented in the company's dossier include only patients who were randomized to treatment arms B and C at the same time. After initiation of the treatment arm nivolumab + platinum-based chemotherapy (arm C), a total of 179 patients were randomly assigned to each of the 2 treatment arms nivolumab + platinum-based chemotherapy and platinum-based chemotherapy. The company's dossier presents the data of a subpopulation with a tumour cell PD-L1 expression ≥ 1% (PD-L1-positive population). This subpopulation comprises 89 patients in each of the 2 arms.

The administration of nivolumab is in line with the Summary of Product Characteristics (SPC). The treatment options for platinum-based chemotherapy in the intervention arm were cisplatin + gemcitabine (for squamous cell carcinoma), cisplatin + pemetrexed (for non-squamous cell carcinoma), or carboplatin + paclitaxel. In the comparator arm, the investigator was able to choose from among the options provided for the intervention arm as well as 2 other treatment regimens: cisplatin + vinorelbine and cisplatin + docetaxel. Furthermore, patients with documented reasons for ineligibility for cisplatin treatment were allowed to receive carboplatin instead of cisplatin.

In the intervention and comparator arms, neoadjuvant treatment was administered for up to three 3-week cycles or until the occurrence of unacceptable toxicity or discontinuation of treatment as decided by the investigator or the patient. Within 6 weeks of the end of neoadjuvant treatment, patients who were deemed operable underwent surgical removal of the tumour. Subsequent optional adjuvant therapy, consisting of up to four 3-week cycles of chemotherapy and/or radiotherapy, was administered at the investigator's discretion.

The primary outcomes of the study are event-free survival (EFS) and pathological complete response (pCR). Patient-relevant secondary outcomes were overall survival, health status, and adverse events (AEs).

Assessment of the evidence presented by the company

The CheckMate 816 study presented by the company is unsuitable for deriving conclusions on the added benefit of nivolumab + platinum-based chemotherapy in comparison with the ACT for the research question of the present benefit assessment. This is due primarily to the study inadequately implementing the ACT. This is explained below.

Inadequate implementation of the ACT

For adult patients with resectable NSCLC with tumour cell PD-L1 expression ≥ 1% who are at a high risk of recurrence, the G-BA has defined the ACT of individualized therapy taking into account tumour stage, the presence/absence of a Pancoast tumour, and the feasibility of

R0 resection. The investigator is to select the most suitable treatment option for the individual patient from neoadjuvant systemic chemotherapy or simultaneous radiochemotherapy.

In the CheckMate 816 study, all included patients received neoadjuvant systemic chemotherapy, while simultaneous radiochemotherapy was not offered. According to the guidelines, for patients with stage IIIA NSCLC, simultaneous radiochemotherapy is an equally suitable treatment option as neoadjuvant systemic chemotherapy. Simultaneous radiochemotherapy may also be an option for patients with advanced tumour stages and potential R0 resectability. For patients with Pancoast tumour, who, according to the company, were excluded from the study, simultaneous radiochemotherapy is the treatment of first choice and is hence superior to neoadjuvant systemic chemotherapy.

The equivalence of the 2 treatment options – neoadjuvant systemic chemotherapy versus simultaneous radiochemotherapy – for the majority of study participants (e.g. those in stage IIIA) is insufficient justification for considering 1 of the 2 options as the most suitable treatment and offering only this option in the study. Regarding patients in stage IIIA, which account for approximately 60% of the PD-L1-positive population, it remains unclear for how many individual patients neoadjuvant systemic chemotherapy is the best therapy.

Furthermore, guidelines recommend simultaneous radiochemotherapy for patients with Pancoast tumours. Presumably, however, very few patients, if any, with Pancoast tumours were enrolled because the study's inclusion criteria require tumour resectability and, according to the German Society for Haematology and Medical Oncology (DGHO), a local surgical procedure is impossible in many patients with Pancoast tumour.

Irrespective of this, neoadjuvant systemic therapy as in individualized therapy as defined by the G-BA has not been implemented in the majority of patients in the subpopulation presented by the company. In the context of neoadjuvant systemic chemotherapy, the G-BA specifies 2 treatment regimens as the ACT, specifically cisplatin + vinorelbine and cisplatin + paclitaxel (only for advanced-stage patients). In the comparator arm of the CheckMate 816 study, the investigator was able to choose from 5 different treatment regimens: cisplatin + vinorelbine, cisplatin + gemcitabine (for squamous cell carcinoma), cisplatin + pemetrexed (for non-squamous cell carcinoma), cisplatin + docetaxel, and carboplatin + paclitaxel. This means that the ACT defined by the G-BA has only been implemented for the proportion of patients who received cisplatin + vinorelbine. Module 4 W does not state the proportion of patients in the PD-L1-positive population (N = 89). However, the study report shows that in the comparator arm of the entire study population receiving treatment (N = 176), 13 patients received cisplatin + vinorelbine. Thus, a maximum of 13 out of 89 patients in the comparator arm were treated in accordance with the G-BA's ACT and received cisplatin + vinorelbine. The company has not presented an analysis which includes only these patients in the comparator arm, and doing so would not be appropriate for the following reasons: In Module 4 W, the

company states that the platinum component was selected by the investigator prior to randomization and that the reasons for the selection were documented. However, it is not clear from the study documents or Module 4 W whether allocation to the chemotherapy component (gemcitabine, pemetrexed, paclitaxel, docetaxel, vinorelbine) took place before or after randomization. Allocation to the chemotherapy component before randomization would have been possible if, for instance, all patients had been assigned a chemotherapy before randomization for the event that they were later allocated to the comparator arm. However, according to the European Public Assessment Report (EPAR), the chemotherapy regimen was assigned by the investigator only after randomization. Therefore, a comparison based on all intervention-arm patients with a PD-L1 expression ≥ 1% versus only those control-arm patients with a PD-L1 expression ≥ 1% who were treated with the ACT specified by the G-BA would not be appropriate, as this would violate the randomization. The CheckMate 816 study is therefore not suitable for drawing conclusions regarding the added benefit of nivolumab + platinum-based chemotherapy in the neoadjuvant treatment of resectable NSCLC in adults with tumour cell PD-L1 expression ≥ 1% and a high risk of recurrence.

Results on added benefit

Since no data for comparison with the ACT are available for the present research question, there is no hint of an added benefit of nivolumab + platinum-based chemotherapy versus the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 summarizes the result of the assessment of added benefit of nivolumab + platinum-based chemotherapy in comparison with the ACT.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: 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 directly comparative study, 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.

I 2 Research question

The aim of this report is to assess the added benefit of nivolumab in combination with platinum-based chemotherapy (hereinafter referred to as nivolumab + platinum-based chemotherapy) compared with the ACT for the neoadjuvant treatment of resectable NSCLC with tumour cell PD-L1 expression ≥ 1% in adults at high risk of recurrence.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of nivolumab in combination with platinum-based chemotherapy

Therapeutic indication	**ACT[a]**
Neoadjuvant treatment of resectable NSCLC with PD-L1 expression in ≥ 1% of tumour cells in 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
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 directly comparative study, 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	

In the context of the specification of the ACT, the G-BA points out that the available guidelines and scientific-medical societies (Drug Commission of the German Medical Association) in accordance with § 35a (7), sentence 4 SGB V list both approved and unapproved drugs for the neoadjuvant and adjuvant treatment of resectable NSCLC. According to the BSG comments on the judgement of 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 as ACTs in the narrower sense of § 2 (1), sentence 3, § 12 SGB V.

In agreement with the G-BA, the company initially considered the ACT to be individualized therapy with a choice of neoadjuvant systemic chemotherapy or simultaneous radiochemotherapy, taking into account the tumour stage, the presence/absence of a Pancoast tumour, and the feasibility of R0 resection. However, when listing individual treatment regimens in the context of neoadjuvant systemic chemotherapy and simultaneous radiochemotherapy, the company deviates from the ACT specified by the G-BA. For neoadjuvant systemic chemotherapy, the company lists ACT options other than those mentioned by the G-BA: cisplatin in combination with either etoposide, docetaxel, gemcitabine, or pemetrexed (only for non-squamous cell carcinoma) and, for patients at increased risk of cisplatin-induced side effects, carboplatin in combination with either vinorelbine, paclitaxel, etoposide, docetaxel, gemcitabine, or pemetrexed (only for non-squamous cell carcinoma). For simultaneous radiochemotherapy, the company likewise lists ACT options other than those specified by the G-BA: cisplatin in combination with either etoposide or pemetrexed (only for non-squamous cell carcinoma) and, for patients at increased risk of cisplatin-induced side effects, carboplatin in combination with either vinorelbine, etoposide, or pemetrexed (only for non-squamous cell carcinoma). In addition, the company argues that to answer the research questions, patients with Pancoast tumour must be distinguished from those without Pancoast tumour.

The present assessment is implemented in comparison with the ACT specified by the G-BA (see Table 4).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of any added benefit. This concurs with the company’s inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on nivolumab (status: 7 June 2023)
- bibliographical literature search on nivolumab (last search on 7 June 2023)
- search in trial registries / trial results databases for studies on nivolumab (last search on 7 June 2023)
- search on the G-BA website for nivolumab (last search on 7 June 2023)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 12 August 2023); for search strategies, see I Appendix A of the full dossier assessment

The check of the completeness of the study pool identified no relevant RCTs for the direct comparison of nivolumab + platinum-based chemotherapy versus the ACT.

The company, in contrast, has identified the RCT CA209-816 (hereinafter CheckMate 816) [3-7]. However, the company's search in PubMed and Central did not include sufficient variations of the search terms for the intervention, resulting in the failure to identify the RCT CheckMate 816 based on the company's search strategies in said databases. Furthermore, regarding the strategy for searching the EU Clinical Trial Register, some of the compound search terms presented by the company were stated without brackets, causing the system to disregard them as compound search terms or phrases. Experience shows that such searches cause errors in trial registers and do not lead to the intended results.

The analyses on the CheckMate 816 study presented by the company are disregarded for the present benefit assessment. This is due to the fact that the ACT defined by the G-BA has not been adequately implemented in the study's comparator arm (for detailed reasons, see the following sections).

I 3.1 Evidence presented by the company – CheckMate 816 study

The CheckMate 816 study is an open-label, multicentre RCT comparing nivolumab + platinum-based chemotherapy versus platinum-based chemotherapy in the neoadjuvant treatment of NSCLC.

The study included adult patients with histologically confirmed and resectable NSCLC in stage IB (tumour size ≥ 4 cm), II, or IIIA, each as per IASLC staging criteria, 7th edition [8]. The

approved therapeutic indication for nivolumab + platinum-based chemotherapy for the neoadjuvant treatment of NSCLC includes patients with a high risk of recurrence and, according to the selection criteria listed in Section 5.1 of the SPC, only stages II to IIIA as per IASLC staging criteria, 7th edition [8,9]. CheckMate 816 participants in stage IB (≥ 4 cm) are therefore not covered by the authorization or the present research question. However, at 9 patients, this affects only a small proportion (5%) of the PD-L1-positive population presented by the company (N = 178; see below). While the study was ongoing, the staging criteria and the associated stages also changed from the 7th edition of the IASLC to the current 8th edition [10]. The parallel existence of both editions may have led to minor discrepancies in staging and patient enrolment. For example, patients with a tumour size ≥ 4 cm who were classified as stage IB as per the 7th edition are now classified as stage II as per the current 8th edition and therefore fall under the present therapeutic indication. Patients with a tumour size and lymph node status of T3-4, N2, in contrast, are in stage IIIA based on the 7th edition but in stage IIIB according to the 8th edition, which is not covered by this therapeutic indication.

Furthermore, patients had to be in good general condition as measured by an ECOG-PS of 0 or 1 at baseline. The study excluded patients with known EGFR mutations or ALK translocation as well as those with previous chemotherapy or other cancer therapy in an early stage of NSCLC. Tumour cell PD-L1 expression had to be determined for patients to be enrolled in the study. This was done by a central laboratory using the PD-L1 IHC 28-8 pharmDx kit (Dako).

The original study protocol provided for randomization in a 1:1 ratio to the following 2 treatment arms: nivolumab + ipilimumab (arm A) versus platinum-based chemotherapy (arm B). The revised protocol 02 dated 6 July 2017 introduced a 3rd treatment arm (arm C, nivolumab + platinum-based chemotherapy), and randomization was thereafter carried out in a 1:1:1 ratio. As of protocol revision 03 dated 21 September 2018, no further patients were randomized into to the nivolumab + ipilimumab arm, with randomization then being carried out only into the 2 remaining arms in a 1:1 ratio. The analyses presented by the company in the dossier include only patients who were randomized to treatment arms B and C at the same time. After initiation of the treatment arm nivolumab + platinum-based chemotherapy (arm C), a total of 179 patients were randomly assigned to each of the 2 treatment arms nivolumab + platinum-based chemotherapy and platinum-based chemotherapy. Randomization was stratified by tumour cell PD-L1 expression (≥ 1% versus < 1%, including nonquantifiable), disease stage at baseline (IIB/II versus IIIA), and sex (male versus female). The company's dossier presents the data of a subpopulation with a tumour cell PD-L1 expression ≥ 1% (PD-L1-positive population). This subpopulation comprises 89 patients in each of the 2 arms. The company has refrained from restricting the population as per authorization to disease stages II to IIIA as per IASLC 7th edition [8]. According to the company, no patients with Pancoast tumour were included in the study.

Nivolumab was administered in compliance with the SPC [9]. In the intervention arm, the treatment options for platinum-based chemotherapy were cisplatin + gemcitabine (for squamous cell carcinoma), cisplatin + pemetrexed (for non-squamous cell carcinoma), or carboplatin + paclitaxel. In the comparator arm, the investigator was able to choose from among the options provided for the intervention arm as well as 2 other treatment regimens: cisplatin + vinorelbine and cisplatin + docetaxel. The chemotherapy regimen of carboplatin + paclitaxel was introduced in the intervention and comparator arms only by revised protocol 03 dated 21 September 2018, and the selection did not require any additional justification by the investigator. Furthermore, patients with documented reasons for ineligibility for cisplatin treatment were allowed to receive carboplatin instead of cisplatin.

In the intervention and comparator arms, neoadjuvant treatment was administered for up to three 3-week cycles or until the occurrence of unacceptable toxicity or discontinuation of treatment as decided by the investigator or the patient. Within 6 weeks of the end of neoadjuvant treatment, patients who were deemed operable underwent surgical removal of the tumour. Subsequent optional adjuvant therapy, consisting of up to four 3-week cycles of chemotherapy and/or radiotherapy, was administered at the investigator's discretion. Possible adjuvant treatment regimens corresponded to the chemotherapy options for the neoadjuvant treatment in the comparator arm (see above). Of all patients in the study who received neoadjuvant therapy (176 per treatment arm), 35 patients (19.9%) in the intervention arm also received adjuvant therapy, while this figure was markedly higher in the comparator arm with 56 patients (31.8%) [3].

The primary outcomes of the study were EFS and pCR. Patient-relevant secondary outcomes were overall survival, health status, and AEs.

A total of 3 predefined data cutoffs are available for the CheckMate816 study:

- 1st data cutoff with data lock on 16 September 2020: analysis of pCR
- 2nd data cutoff with data lock on 20 October 2021: 1st interim analysis on EFS and overall survival
- 3rd data cutoff with data lock on 14 October 2022: 2nd interim analysis on EFS and overall survival

Further information on the CheckMate 816 study can be found in I Appendix B of the full dossier assessment.

I 3.2 Assessment of the evidence presented by the company

The CheckMate 816 study presented by the company is unsuitable for deriving conclusions on the added benefit of nivolumab + platinum-based chemotherapy in comparison with the ACT

for the research question of the present benefit assessment. This is due primarily to the study inadequately implementing the ACT. This is explained below.

I 3.2.1 Insufficient implementation of the ACT

For adult patients with resectable NSCLC with tumour cell PD-L1 expression ≥ 1% who are at a high risk of recurrence, the G-BA has defined the ACT of individualized therapy taking into account tumour stage, the presence/absence of a Pancoast tumour, and the feasibility of R0 resection. The investigator is to select the most suitable treatment option for the individual patient from neoadjuvant systemic chemotherapy or simultaneous radiochemotherapy. Additionally, the G-BA points out that in a directly comparative study, 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.

In the CheckMate 816 study, all included patients received neoadjuvant systemic chemotherapy, while simultaneous radiochemotherapy was not offered. As per the guidelines [11,12] for patients with stage IIIA NSCLC, simultaneous radiochemotherapy is an equally suitable treatment option as neoadjuvant systemic chemotherapy. Simultaneous radiochemotherapy may also be an option for patients with advanced tumour stages and potential R0 resectability. For patients with Pancoast tumour, who according to the company were excluded from the study, simultaneous radiochemotherapy is the treatment of first choice and is hence superior to neoadjuvant systemic chemotherapy. The company deduces that the neoadjuvant systemic chemotherapy administered in the RCT CheckMate 816 is the most suitable ACT option for all included patients.

This is not appropriate. The equivalence of the 2 treatment options – neoadjuvant systemic chemotherapy versus simultaneous radiochemotherapy – in the majority of study participants (e.g. those in stage IIIA) is insufficient justification for deeming 1 of the 2 options as the most suitable treatment and offering only this option in the study. For the implementation of individualized therapy in accordance with the ACT specified by the G-BA, the investigator should have been able to decide between the 2 options on an individualized basis after medically assessing the patient. Regarding patients in stage IIIA, which account for approximately 60% of the PD-L1-positive population, it remains unclear for how many individual patients neoadjuvant systemic chemotherapy is the best therapy.

Furthermore, the guidelines recommend simultaneous radiochemotherapy for patients with Pancoast tumours [11-13]. In alignment with the study's inclusion and exclusion criteria, such patients were not generally excluded from study participation. The study's inclusion criteria did, however, require resectability of the tumour. Hence, it can be assumed that only very few patients with Pancoast tumours were included; after all, according to the DGHO [13], a local

surgical procedure is impossible for many patients with Pancoast tumours. Furthermore, the S3 guideline [11] and the literature [14,15] describe this clinical picture as rare or estimate it to represent < 5% of all bronchial carcinomas.

Irrespective of this, neoadjuvant systemic therapy as in individualized therapy as defined by the G-BA has not been implemented in the majority of patients in the subpopulation presented by the company. In the context of neoadjuvant systemic chemotherapy, the G-BA specifies 2 treatment regimens as ACTs, namely cisplatin + vinorelbine and cisplatin + paclitaxel (only for advanced-stage patients). In the comparator arm of the CheckMate 816 study, the investigator was able to choose from 5 different treatment regimens: cisplatin + vinorelbine, cisplatin + gemcitabine (for squamous cell carcinoma), cisplatin + pemetrexed (for non-squamous cell carcinoma), cisplatin + docetaxel, and carboplatin + paclitaxel. This means that the ACT defined by the G-BA has been implemented only in the proportion of patients who received cisplatin + vinorelbine. Module 4 W does not state the proportion of patients in the PD-L1-positive population (N = 89). However, the study report shows that in the comparator arm of the entire study population receiving treatment (N = 176), 13 patients received cisplatin + vinorelbine. Thus, a maximum of 13 out of 89 patients in the comparator arm were treated in accordance with the G-BA's ACT and received cisplatin + vinorelbine. The company has not presented an analysis exclusively for these patients in the comparator arm, and doing so would not be appropriate for the following reasons: In Module 4 W, the company states that the platinum component was selected by the investigator prior to randomization and that the reasons for the selection were documented. It can also be deduced from information provided in the electronic Case Report Form (eCRF) on the allocation of treatment that the choice between carboplatin and cisplatin was made during screening, i.e. before randomization. However, it is not clear from the study documents or Module 4 W whether allocation to the chemotherapy component (gemcitabine, pemetrexed, paclitaxel, docetaxel, vinorelbine) took place before or after randomization. Allocation to the chemotherapy component before randomization would have been possible if, for instance, all patients had been assigned a chemotherapy before randomization for the event that they were later allocated to the comparator arm. However, according to the EPAR [16], the chemotherapy regimen was assigned by the investigator only after randomization. Therefore, a comparison based on all patients with a PD-L1 expression ≥ 1% of the intervention arm versus only those patients with a PD-L1 expression ≥ 1% of the control arm who received treatment according to the G-BA's ACT would not be appropriate, as this would violate the randomization.

I 3.2.2 Effect on overall survival not transferable

For the overall survival outcome, the CheckMate 816 study showed a significant difference in favour of nivolumab + platinum-based chemotherapy over platinum-based chemotherapy (hazard ratio [95% confidence interval]; p-value: 0.37 [0.19; 0.71]; 0.002) for the subpopulation presented by the company at the data cutoff with the 14 October 2022 lock

date. This would be interpreted as being of considerable extent. Despite this effect, no added benefit can be derived for nivolumab + platinum-based chemotherapy in this therapeutic indication. This is because it is unclear whether the observed effect is transferable to the dossier assessment's research question with the ACT specified by the G-BA since the proportion of patients who received cisplatin + vinorelbine as neoadjuvant systemic chemotherapy is certainly < 15%, possibly even ≤ 10% after subtracting patients with PD-L1 expression ≤ 1%. To check the transferability of the observed effects, it would be conceivable to conduct subgroup analyses regarding the treatments received. In the CheckMate 816 study, such subgroup analyses are available only for the platinum component assigned by the investigator prior to randomization. However, these analyses do not contribute to answering the question of transferability. As explained above, it is not possible to conduct valid subgroup analyses on the combination partner of the platinum component (i.e. vinorelbine versus other combination partners) due to the fact that allocation took place only after randomization and doing so would lead to a violation of randomization. Hence, insufficient information is available for justifying the transferability of results.

I 4 Results on added benefit

For assessing the added benefit of nivolumab + platinum-based chemotherapy in the neoadjuvant treatment of resectable NSCLC in adult patients with tumour cell PD-L1 expression ≥ 1% and high risk of recurrence, no data are available for comparison with the ACT. This results in no hint of an added benefit of nivolumab + platinum-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of nivolumab + platinum-based chemotherapy in comparison with the ACT.

Table 5: 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 assessment described above differs from that of the company, which derived an indication of considerable added benefit of nivolumab + platinum-based chemotherapy compared with the ACT based on the results of the CheckMate 816 study for patients without Pancoast tumour. The company does not claim any added benefit for patients with Pancoast tumour.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-74.html.