Pembrolizumab (NSCLC, neoadjuvant + adjuvant)

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

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

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

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Part I: Benefit assessment

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[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
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
EFS	event-free survival
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TPS	Tumour Proportion Score

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 pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment. 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 30 April 2024.

Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment, in comparison with the appropriate comparator therapy (ACT) in adult patients with resectable non-small cell lung cancer (NSCLC) at high risk of recurrence.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant)

Research question	Therapeutic indication	ACT[a]
1	Adult patients with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment	Neoadjuvant[b]: nivolumab in combination with platinum-based therapy Adjuvant: BSC[c]
2	Adult patients with resectable non-small cell lung cancer with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment	Neoadjuvant[b]: individualized treatment selected from ▪ pre-operative (neoadjuvant) systemic chemotherapy selected from ▫ cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and ▫ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and ▪ simultaneous radiochemotherapy with platinum-based (cisplatin or carboplatin) combination chemotherapy taking into account the tumour stage, the tumour histology, the presence of a Pancoast tumour and the feasibility of an R0 resection, as well as the prerequisites for the use of carboplatin Adjuvant: BSC[c]

a. Presented is the respective ACT specified by the G-BA.
b. Comments of the G-BA:
- The ACT was determined in the present therapeutic indication on the condition that the decision in favour of neoadjuvant therapy was made in the present therapeutic indication.
- 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). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
- Cisplatin and carboplatin, each in combination with a third-generation cytostatic agent, are not approved for the neoadjuvant treatment of resectable NSCLC. The use of cisplatin or carboplatin in combination with vinorelbine, paclitaxel, docetaxel, gemcitabine, or pemetrexed is medically necessary for the neoadjuvant treatment of patients with NSCLC with tumour cell PD-L1 expression < 1%. According to the generally recognised state of medical knowledge in the therapeutic indication to be assessed, off-label use is considered the therapy standard.

c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

For better readability, the research questions defined by the G-BA are abbreviated below as patients with tumour cell programmed death ligand 1 (PD-L1) expression ≥ 1% (research question 1) or patients with tumour cell PD-L1 expression < 1% (research question 2).

On 7 May 2024, the G-BA adjusted the ACT after submission of the dossier by the company (19 April 2024) as shown in Table 2. In its Module 3 A, the company referred to the previously defined ACT of 18 November 2022. This was an individualized treatment that referred to the entire patient population in the present therapeutic indication in only one research question.

The company claims to have followed the ACT specified by the G-BA. The information provided by the company in the dossier relates to the original ACT. Therefore, the company only addressed one research question in its dossier. The present assessment is implemented in comparison with the ACT specified by the G-BA (see Table 2).

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) are used to derive added benefit. This concurs with the company's inclusion criteria.

Results

Evidence presented by the company – KEYNOTE 671 study

The KEYNOTE 671 study is an ongoing double-blind RCT evaluating pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant) compared to placebo in combination with platinum-based chemotherapy (neoadjuvant) and subsequent placebo monotherapy (adjuvant). It included adult patients with resectable stage II, IIIA or IIIB NSCLC (N2 only). Eligible patients were not allowed to have received any prior NSCLC therapy.

A total of 797 patients were enrolled in the study. Of these, 397 patients were randomized to the intervention arm and 400 to the comparator arm. The study documents show that 289 (36%) of the patients included had tumour cell PD-L1 expression < 1% and 508 (64%) had tumour cell PD-L1 expression ≥ 1%.

Patients in the intervention arm received 4 cycles of pembrolizumab in the neoadjuvant treatment phase. A placebo was administered in the comparator arm. In addition, patients in both treatment arms received platinum-based chemotherapy during the neoadjuvant treatment phase. For patients with squamous NSCLC, this therapy consisted of cisplatin in combination with gemcitabine and for patients with non-squamous NSCLC, cisplatin in combination with pemetrexed. After surgical removal of the tumour, patients in the intervention arm received pembrolizumab for 13 cycles, while a placebo was administered in the comparator arm. The KEYNOTE 671 study generally allowed concomitant treatments.

Treatment was continued until completion of therapy according to protocol, until disease progression, occurrence of unacceptable toxicity, or treatment discontinuation due to a medical decision or the patient's decision. After completion of adjuvant therapy, patients are followed up on an outcome-specific basis, but at most until either death, discontinuation of participation in the study, or end of study.

Primary outcomes of the KEYNOTE 671 study are “event-free survival (EFS)” and “overall survival”. Further patient-relevant outcomes are recorded in the categories of morbidity, health-related quality of life and side effects.

In its dossier, the company presented the results of the total population of the KEYNOTE 671 study.

KEYNOTE 671 study unsuitable for the benefit assessment

Based on the information available, the KEYNOTE 671 study presented by the company is not suitable for assessing the added benefit of pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant) in adult patients with resectable NSCLC with tumour cell PD-L1 expression ≥ 1% or < 1% at high risk of recurrence. This is described below and is due in particular to the fact that the treatment of the comparator arm of the KEYNOTE 671 study does not represent an adequate implementation of the ACT for research questions 1 and 2 defined by the G-BA.

Lack of implementation of the appropriate comparator therapy

Patients with tumour cell PD-L1 expression ≥ 1% (research question 1), neoadjuvant treatment

The G-BA has named nivolumab in combination with platinum-based therapy as ACT for patients with tumour cell PD-L1 expression ≥ 1% (research question 1) in neoadjuvant treatment. Nivolumab was not a treatment option in the comparator arm of the KEYNOTE 671 study. Thus, the results of the KEYNOTE 671 study for the subpopulation of patients with tumour cell PD-L1 expression ≥ 1% (research question 1) cannot be used for the benefit assessment because the study failed to implement the ACT.

Patients with tumour cell PD-L1 expression < 1% (research question 2), neoadjuvant treatment

For patients with tumour cell PD-L1 expression < 1% (research question 2), the G-BA has defined individualized treatment with a choice of systemic chemotherapy or simultaneous radiochemotherapy as ACT in neoadjuvant treatment.

In the neoadjuvant phase of the KEYNOTE 671 study, cisplatin in combination with gemcitabine was specified as treatment for patients with squamous NSCLC and cisplatin in combination with pemetrexed for patients with non-squamous NSCLC in the comparator arm.

Therefore, the study failed to implement the ACT because the investigators did not have a choice of several treatment options that would have enabled an individualized treatment decision for each patient. In particular, there was no possibility to select the third-generation cytostatic of the systemic chemotherapy based on an individualized treatment decision. The company did not justify the extent to which gemcitabine and pemetrexed represent the most suitable individualized treatment for the patients included in the study compared to the other third-generation cytostatics (vinorelbine, docetaxel and paclitaxel) named by the G-BA in its determination of the ACT.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment in comparison with 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 presents a summary of the probability and extent of the added benefit of pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment.

[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: Pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant) – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Adult patients with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment	Neoadjuvant[b]: nivolumab in combination with platinum-based therapy Adjuvant: BSC[c]	Added benefit not proven
2	Adult patients with resectable non-small cell lung cancer with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment	Neoadjuvant[b]: individualized treatment selected from ▪ pre-operative (neoadjuvant) systemic chemotherapy selected from ▫ cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and ▫ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and ▪ simultaneous radiochemotherapy with platinum-based (cisplatin or carboplatin) combination chemotherapy taking into account the tumour stage, the tumour histology, the presence of a Pancoast tumour and the feasibility of an R0 resection, as well as the prerequisites for the use of carboplatin Adjuvant: BSC[c]	Added benefit not proven

Table 3: Pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant) – probability and extent of added benefit (multipage table)

a. Presented is the respective ACT specified by the G-BA.
b. Comments of the G-BA:
- The ACT was determined in the present therapeutic indication on the condition that the decision in favour of neoadjuvant therapy was made in the present therapeutic indication.
- 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). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
- Cisplatin and carboplatin, each in combination with a third-generation cytostatic agent, are not approved for the neoadjuvant treatment of resectable NSCLC. The use of cisplatin or carboplatin in combination with vinorelbine, paclitaxel, docetaxel, gemcitabine, or pemetrexed is medically necessary for the neoadjuvant treatment of patients with NSCLC with tumour cell PD-L1 expression < 1%. According to the generally recognised state of medical knowledge in the therapeutic indication to be assessed, off-label use is considered the therapy standard.

c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment, in comparison with the appropriate comparator therapy (ACT) in adult patients with resectable non-small cell lung cancer (NSCLC) at high risk of recurrence.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant) (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Adult patients with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment	Neoadjuvant[b]: nivolumab in combination with platinum-based therapy Adjuvant: BSC[c]
2	Adult patients with resectable non-small cell lung cancer with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment	Neoadjuvant[b]: individualized treatment selected from ▪ pre-operative (neoadjuvant) systemic chemotherapy selected from ▫ cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and ▫ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and ▪ simultaneous radiochemotherapy with platinum-based (cisplatin or carboplatin) combination chemotherapy taking into account the tumour stage, the tumour histology, the presence of a Pancoast tumour and the feasibility of an R0 resection, as well as the prerequisites for the use of carboplatin Adjuvant: BSC[c]

Table 4: Research questions of the benefit assessment of pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant) (multipage table)

Research question	Therapeutic indication	ACT[a]

a. Presented is the respective ACT specified by the G-BA.
b. Comments of the G-BA:
- The ACT was determined in the present therapeutic indication on the condition that the decision in favour of neoadjuvant therapy was made in the present therapeutic indication.
- 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). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
- Cisplatin and carboplatin, each in combination with a third-generation cytostatic agent, are not approved for the neoadjuvant treatment of resectable NSCLC. The use of cisplatin or carboplatin in combination with vinorelbine, paclitaxel, docetaxel, gemcitabine, or pemetrexed is medically necessary for the neoadjuvant treatment of patients with NSCLC with tumour cell PD-L1 expression < 1%. According to the generally recognised state of medical knowledge in the therapeutic indication to be assessed, off-label use is considered the therapy standard.

c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

For better readability, the research questions defined by the G-BA are abbreviated below as patients with tumour cell programmed death ligand 1 (PD-L1) expression ≥ 1% (research question 1) or patients with tumour cell PD-L1 expression < 1% (research question 2).

On 7 May 2024, the G-BA adjusted the ACT after submission of the dossier by the company (19 April 2024) as shown in Table 4. In its Module 3 A, the company referred to the previously defined ACT of 18 November 2022. This was an individualized treatment that referred to the entire patient population in the present therapeutic indication in only one research question.

The company claims to have followed the ACT specified by the G-BA. The information provided by the company in the dossier relates to the original ACT. Therefore, the company only addressed one research question in its dossier. 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 are used to derive added benefit. This concurs with the company's inclusion criteria.

Since no suitable data are available for any of the research questions named by the G-BA, the assessment below is performed in a joint section of the report (see Chapters I 3 to I 5).

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 pembrolizumab (status: 7 February 2024)
- bibliographical literature search on pembrolizumab (last search on 5 March 2024)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 5 March 2024)
- search on the G-BA website for pembrolizumab (last search on 15 March 2024)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 8 May 2024); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check.

This deviates from the assessment of the company, whose information retrieval identified the KEYNOTE 671 study [3] and included it in its study pool. However, the KEYNOTE 671 study is not suitable for the benefit assessment of pembrolizumab because the study failed to implement the ACT specified by the G-BA. This is justified below.

KEYNOTE 671 study

The characteristics of the KEYNOTE 671 study are presented in I Appendix B of the full dossier assessment. The KEYNOTE 671 study is an ongoing double-blind RCT evaluating pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant) compared to placebo in combination with platinum-based chemotherapy (neoadjuvant) and subsequent placebo monotherapy (adjuvant). It included adult patients with resectable stage II, IIIA or IIIB NSCLC (N2 only). Eligible patients were not allowed to have received any prior NSCLC therapy. Further exclusion criteria were the presence of a Pancoast tumour, a large-cell neuroendocrine lung carcinoma or a sarcomatous tumour.

Randomization was performed in a 1:1 ratio and was stratified by tumour stage (II vs. III), PD-L1 status (Tumour Proportion Score [TPS] < 50% vs. TPS ≥ 50%), histology (squamous vs. non-squamous) and region (East Asia vs. rest of the world). The KEYNOTE 671 study included a total of 797 patients, 397 in the intervention arm and 400 in the comparator arm. The study documents show that 289 (36%) of the patients included had tumour cell PD-L1 expression < 1% and 508 (64%) had tumour cell PD-L1 expression ≥ 1%.

Patients in the intervention arm received 4 cycles of pembrolizumab in the neoadjuvant treatment phase in accordance with the Summary of Product Characteristics (SPC) [4]. A placebo was administered in the comparator arm. In addition, patients in both treatment arms received platinum-based chemotherapy during the neoadjuvant treatment phase. For patients with squamous NSCLC, this therapy consisted of cisplatin in combination with gemcitabine and for patients with non-squamous NSCLC, cisplatin in combination with pemetrexed. The tumour was surgically removed within 4 to 8 weeks after the last neoadjuvant dose. Following R0 resection, the patients entered the adjuvant treatment phase. Patients who have undergone surgery and have positive resectate margins, extracapsular tumour growth of the lymph nodes, or serious residual disease, as well as patients who could not be operated on as planned, should receive radiotherapy before starting the adjuvant treatment phase. Adjuvant therapy should begin 4 to 12 weeks after surgery or 2 to 4 weeks after radiotherapy. Patients in the intervention arm received 13 cycles of pembrolizumab in the adjuvant treatment phase in accordance with the SPC while a placebo was administered in the comparator arm [4]. The KEYNOTE 671 study generally allowed concomitant treatments. Only a few therapies were disallowed, such as other antineoplastic treatments or systemic glucocorticoids, unless they were used for side effect management (see also Table 7 of the full dossier assessment). Patients with local disease progression, metastatic disease, or recurrence completed the study treatment and entered the follow-up phase.

Treatment was continued until completion of therapy according to protocol, until disease progression, occurrence of unacceptable toxicity, or treatment discontinuation due to a medical decision or the patient's decision. After completion of adjuvant therapy, patients are followed up on an outcome-specific basis, but at most until either death, discontinuation of participation in the study, or end of study.

Primary outcomes of the KEYNOTE 671 study are “event-free survival (EFS)” and “overall survival”. Further patient-relevant outcomes are recorded in the categories of morbidity, health-related quality of life and side effects.

To date, there are 2 planned interim analyses for the current KEYNOTE 671 study for the data cut-off 29 July 2022 and data cut-off 10 July 2023. The final data cut-off will take place after approximately 386 patients have died and is expected approximately 96 months after randomization of the first patient.

Lack of implementation of the appropriate comparator therapy

Patients with tumour cell PD-L1 expression ≥ 1% (research question 1), neoadjuvant treatment

The G-BA has named nivolumab in combination with platinum-based therapy as ACT for patients with tumour cell PD-L1 expression ≥ 1% (research question 1) in neoadjuvant treatment. Nivolumab was not a treatment option in the comparator arm of the KEYNOTE 671 study. Thus, the results of the KEYNOTE 671 study for the subpopulation of patients with tumour cell PD-L1 expression ≥ 1% (research question 1) cannot be used for the benefit assessment because the study failed to implement the ACT.

Patients with tumour cell PD-L1 expression < 1% (research question 2), neoadjuvant treatment

For patients with tumour cell PD-L1 expression < 1% (research question 2), the G-BA has defined individualized treatment with a choice of systemic chemotherapy or simultaneous radiochemotherapy as ACT in neoadjuvant treatment.

In the neoadjuvant phase of the KEYNOTE 671 study, cisplatin in combination with gemcitabine was specified as treatment for patients with squamous NSCLC and cisplatin in combination with pemetrexed for patients with non-squamous NSCLC in the comparator arm. Therefore, the study failed to implement the ACT because the investigators did not have a choice of several treatment options that would have enabled an individualized treatment decision for each patient. In particular, there was no possibility to select the third-generation cytostatic of the systemic chemotherapy based on an individualized treatment decision. The company did not justify the extent to which gemcitabine and pemetrexed represent the most suitable individualized treatment for the patients included in the study compared to the other third-generation cytostatics (vinorelbine, docetaxel and paclitaxel) named by the G-BA in its determination of the ACT. Based on the available information, it is not possible to assess the suitability of third-generation cytostatics for individualized treatment. In the current S3 Guideline on the Prevention, Diagnosis, Treatment and Follow-up of Lung Cancer [5], the tumour stage according to the TNM classification is taken into account in the recommendations for the treatment of NSCLC. For example, a combination of cisplatin and a taxane is recommended for neoadjuvant chemotherapy for stage IIIA3 patients. However, no information is available on how many patients in the subpopulation with a tumour cell PD-L1 expression < 1% (research question 2) are classifiable as stage IIIA3.

It was also not possible for the investigators to select carboplatin as the platinum-containing component of the neoadjuvant chemotherapy based on individual factors, as the sole use of cisplatin was prescribed in the KEYNOTE 671 study.

The individualized treatment defined by the G-BA in the ACT also includes the option of simultaneous radiochemotherapy in the neoadjuvant treatment phase. Simultaneous radiochemotherapy in the neoadjuvant treatment phase was disallowed in the KEYNOTE 671 study. However, according to the inclusion criteria of the KEYNOTE 671 study, no patients were included for whom simultaneous radiochemotherapy would have been indicated in the neoadjuvant treatment phase (e.g. patients with Pancoast tumours). The failure to include the possibility of neoadjuvant simultaneous radiochemotherapy therefore is of no consequence for the implementation of the ACT in the KEYNOTE 671 study.

Adjuvant treatment phase

The G-BA specified BSC as the ACT in the adjuvant treatment phase for both research questions. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The KEYNOTE 671 study generally allowed the use of other drugs. Data on concomitant treatments are only available for the total population. Overall, the data for the total population show extensive and balanced use of concomitant non-oncological therapies between the study arms. Patients in the comparator arm received subsequent antineoplastic therapies more frequently than those in the intervention arm. In the adjuvant treatment phase, the ACT BSC is considered to be adequately implemented overall for both research questions.

Analyses presented by the company

In its dossier, the company presented the analyses of the total population of the KEYNOTE 671 study. Results for the subpopulations of patients with a tumour cell PD-L1 expression < 1% or ≥ 1% are only available for individual outcomes. Therefore, a benefit assessment based on the available data would not be possible, irrespective of the failure to implement the ACT.

Conclusion

Due to the limitations described above, the treatment provided to the comparator arm in the KEYNOTE 671 study does not constitute implementation of the ACT defined by the G-BA for research questions 1 and 2. Therefore, the KEYNOTE 671 study presented by the company is not suitable for assessing the added benefit of pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment, in comparison with the ACT in adult patients with resectable NSCLC with tumour cell PD-L1 expression ≥ 1% or < 1% at high risk of recurrence.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment, in comparison with the ACT in adult patients with resectable NSCLC with tumour cell PD-L1 expression ≥ 1% or < 1% at high risk of recurrence. There is no hint of an added benefit of pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment in comparison with the ACT is summarized in Table 5.

Table 5: Pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant) – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment	Neoadjuvant[b]: nivolumab in combination with platinum-based therapy Adjuvant: BSC[c]	Added benefit not proven
2	Adult patients with resectable non-small cell lung cancer with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment	Neoadjuvant[b]: individualized treatment selected from ▪ pre-operative (neoadjuvant) systemic chemotherapy selected from ▫ cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and ▫ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and ▪ simultaneous radiochemotherapy with platinum-based (cisplatin or carboplatin) combination chemotherapy taking into account the tumour stage, the tumour histology, the presence of a Pancoast tumour and the feasibility of an R0 resection, as well as the prerequisites for the use of carboplatin Adjuvant: BSC[c]	Added benefit not proven

Table 5: Pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant) – probability and extent of added benefit (multipage table)

a. Presented is the respective ACT specified by the G-BA.
b. Comments of the G-BA:
- The ACT was determined in the present therapeutic indication on the condition that the decision in favour of neoadjuvant therapy was made in the present therapeutic indication.
- 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). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
- Cisplatin and carboplatin, each in combination with a third-generation cytostatic agent, are not approved for the neoadjuvant treatment of resectable NSCLC. The use of cisplatin or carboplatin in combination with vinorelbine, paclitaxel, docetaxel, gemcitabine, or pemetrexed is medically necessary for the neoadjuvant treatment of patients with NSCLC with tumour cell PD-L1 expression < 1%. According to the generally recognised state of medical knowledge in the therapeutic indication to be assessed, off-label use is considered the therapy standard.

c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

The assessment described above deviates from that of the company, which derived an indication of major added benefit.

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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