Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)
Pembrolizumab (new therapeutic indication: non-small cell lung carcinoma, adjuvant treatment, after prior chemotherapy)

of 17 October 2024

Contents

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient pembrolizumab (Keytruda) was listed for the first time on 15 August 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 14 July 2023, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for pembrolizumab in the therapeutic indication "Monotherapy for the adjuvant treatment of adults with tumour stage IB (T2 ≥ 4 cm), II or IIIA non-small cell lung carcinoma who have undergone complete resection" in accordance with Section 35a paragraph 5b SGB V.

At its session on 17 August 2023, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the other therapeutic indication of the therapeutic indication covered by the application, at the latest six months after the first

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relevant date. The marketing authorisation for the other therapeutic indication covered by the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

On 12 October 2023, pembrolizumab received an extension of the marketing authorisation for the therapeutic indication "Monotherapy for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy". The extension of the marketing authorisation for the therapeutic indication "Combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults" was granted on 25.03.2024. Both extensions of the marketing authorisation are classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 19 April 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the therapeutic indication

"Monotherapy for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy".

Based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, the G-BA decided on the question on whether an additional benefit of luspatercept compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of pembrolizumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Pembrolizumab (Keytruda) in accordance with the product information

Keytruda as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy.

Therapeutic indication of the resolution (resolution of 17.10.2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with non-small cell lung carcinoma at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment

Appropriate comparator therapy for pembrolizumab as monotherapy:

- Monitoring wait-and-see approach

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal

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product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

on 1. In addition to pembrolizumab, the active ingredients atezolizumab, cisplatin, osimertinib and vinorelbine are approved in the therapeutic indication to be considered.

on 2. For patients with completely resected NSCLC, adjuvant cisplatin-based chemotherapy may be followed by radiotherapy in individual cases. However, this is not applied on a regular basis. The G-BA therefore expects for the present treatment setting that radiotherapy is eligible only in individual cases for a few patients and is therefore not included among the standard therapies in the therapeutic indication.

on 3. In the therapeutic indication to be considered, there are two resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- atezolizumab (resolution of 5 January 2023)

- osimertinib (resolution of 16 December 2021)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see “Information on Appropriate Comparator Therapy”).

The approved active ingredients atezolizumab and osimertinib are available for the adjuvant treatment of patients with completely resected NSCLC.

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These active ingredients are also named in the guidelines for patients with completely resected NSCLC in stages II or IIIA after prior adjuvant platinum-based chemotherapy.

Accordingly, osimertinib can be used following adjuvant chemotherapy after complete tumour resection in line with the S3 guideline recommendation for patients, whose tumours have mutations of the epidermal growth factor receptor (EGFR) as deletion in exon 19 or substitution mutation in exon 21 (L858R).

In the benefit assessment of osimertinib, an indication of a non-quantifiable additional benefit was found for patients who had previously undergone chemotherapy or who were ineligible for chemotherapy compared to "monitoring wait-and-see approach" (resolution of 16.12.2021). The validity of the resolution was limited to 1 July 2024. The active ingredient osimertinib is currently undergoing a new benefit assessment procedure.

The active ingredient atezolizumab represents another treatment option in the adjuvant therapy of NSCLC. Atezolizumab as monotherapy is approved after complete resection and platinum-based chemotherapy in patients at a high risk of recurrence and whose tumours have PD-L1 expression on ≥ 50% of the tumour cells and who do not have EGFR-mutated or ALK-positive NSCLC.

According to the S3 guideline, patients with PD-L1 expression ≥ 50% (without EGFR or ALK mutation) and R0 resection after adjuvant chemotherapy should be offered adjuvant therapy with atezolizumab for 1 year.

In their written statement, the scientific-medical societies and the AkdÄ also recommend atezolizumab (for PD-L1 expression ≥ 50% and exclusion of EGFR or ALK mutation, for complete resection after adjuvant chemotherapy) or osimertinib (for EGFR mutation del19 or L858R, for complete resection after adjuvant chemotherapy).

In the benefit assessment of atezolizumab, a hint for a non-quantifiable additional benefit over "monitoring wait-and-see approach" was identified (resolution of 5 January 2023). The validity of the resolution was limited to 1 October 2024. The active ingredient atezolizumab is currently undergoing a new benefit assessment procedure.

Against the background of the available evidence on osimertinib and atezolizumab, and particularly in view of the fact that further clinical data are being assessed for both atezolizumab and osimertinib, the significance of these active ingredients cannot be conclusively assessed.

For patients who do not have a mutation in the EGF receptor or a PD-L1 expression < 50%, there is no recommendation for another medicinal or non-medicinal adjuvant treatment.

In the overall assessment and taking into account the existing treatment setting, according to which the patients in the therapeutic indication are considered disease-free, the G-BA determined "monitoring wait-and-see approach" as an appropriate comparator therapy.

The appropriate comparator therapy was determined for stages IB (T ≥ 4cm) to IIIA according to the 8th edition of UICC/AJCC[2].

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

[2] Union for International Cancer Control / American Joint Committee of Cancer

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A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of pembrolizumab is assessed as follows:

An additional benefit is not proven.

Justification:

For the proof of the additional benefit of pembrolizumab, the pharmaceutical company presented the results of a sub-population of the KEYNOTE 091 study started in November 2015.

KEYNOTE 091 is an ongoing, multicentre, triple-blinded, randomised, controlled phase III study comparing pembrolizumab with placebo. Adult patients with pathologically confirmed NSCLC at high risk of recurrence, defined as stage IB (T2a ≥ 4 cm) to IIIA (classification according to the 7th edition of the UICC/AJCC), were enrolled after complete tumour resection (R0 resection) and regardless of histological classification. They should not show any evidence of the disease within 12 weeks prior to randomisation. Patients were enrolled, regardless of their PD-L1 status.

A total of 1,177 patients were randomised in a 1:1 ratio to either treatment with pembrolizumab (N = 590) or placebo (N = 587). The marketing authorisation of pembrolizumab in this therapeutic indication is limited to patients at high risk of recurrence following complete resection and platinum-based chemotherapy. For the benefit assessment, the pharmaceutical company therefore presented the results for the benefit-assessment-relevant sub-population of patients with previous adjuvant chemotherapy. This sub-population includes 506 patients in the pembrolizumab arm and 504 patients in the comparator arm.

The placebo comparison carried out in the KEYNOTE 091 study corresponds sufficiently to implementation of the appropriate comparator therapy "monitoring wait-and-see approach" for the benefit-assessment-relevant sub-population.

The study is being conducted in 206 study sites across Australia, Asia, Europe, North America and South America.

The present benefit assessment is based on the results for the 3rd data cut-off from 24.01.2023.

The enrolment of patients in the KEYNOTE 091 study was based on the 7th edition of the TNM classification according to UICC/AJCC. Based on the current staging of the 8th edition of the TNM classification according to UICC/AJCC, there are some changes in the staging compared to the 7th edition. According to the information provided by the pharmaceutical company, the percentage of patients in the assessment-relevant sub-population, who have stage IIIB tumours according to the current 8th classification, was 5.62%.

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Limitations of the KEYNOTE 091 study

In the KEYNOTE 091 study, the time between tumour resection and adjuvant chemotherapy was longer than 60 days for 18% of patients. According to the guideline recommendation,[3] adjuvant chemotherapy should begin within 60 days of resection once wound healing is complete. Based on the available data, it remains unclear whether a delayed start of adjuvant chemotherapy (> 60 days) has an influence on the observed effects.

Information on the percentage of magnetic resonance imaging (MRI) and/or computerised tomography (CT) scans of the skull to rule out cerebral metastasis is not available.

Extent and probability of the additional benefit

Mortality

Overall survival was defined in the KEYNOTE 091 study as the time between randomisation and death, regardless of the underlying cause of death.

There was no statistically significant difference between the treatment arms.

Based on the information for the total study population on the follow-up therapies used after the end of the study medication, it is particularly striking that relatively few patients with recurrence received subsequent antineoplastic therapy in the comparator arm and that the percentage of checkpoint inhibitors as subsequent therapy was low. Subsequent therapy with checkpoint inhibitors in locally advanced or metastatic stage represents the current therapy standard. Overall, there is uncertainty with regard to the subsequent therapies used.

Morbidity

Recurrences (recurrence rate and disease-free survival)

Patients in the present therapeutic indication are treated with a curative therapeutic approach. The failure of a curative therapeutic approach is fundamentally patient-relevant. The significance of the endpoints on recurrences depends on the extent to which the selected individual components are suitable for adequately reflecting the failure of potential cure by the present curative therapeutic approach.

In the present benefit assessment, recurrences are taken into account in the endpoint of recurrence rate as well as in the endpoint of disease-free survival. Both evaluations include the following events:

- death from any cause
- locoregional recurrence
- distant metastases
- locoregional recurrence and distant metastases
- new malignancy
- not disease-free at the start of the study

[3] Guideline program in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific Medical Societies). S3 guideline - Prevention, diagnostics, therapy and after-care of lung carcinoma; long version 3.0 [online]. 2024 [accessed: 25.09.2024]. URL: https://www.leitlinienprogramm-onkologie.de/leitlinien/lungenkarzinom/

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In the present therapeutic indication, this operationalisation is conditionally suitable to depict a failure of the potential cure by the curative therapeutic approach. It should be noted that patients who were not disease-free at the start of the study should not have been enrolled according to the study protocol. However, the percentage of these patients is < 1% and is therefore of no consequence.

There was a statistically significant difference in favour of pembrolizumab compared to the monitoring wait-and-see approach both for the event rate and for the time-dependent evaluation.

With regard to the results for the recurrence endpoint, it should be noted that at the presented 3rd data cut-off from January 2023 (final data cut-off for the recurrence endpoint) of the KEYNOTE 091 study, there was only a limited observation period with a median observation period of around 35 months. A longer observation period would have been necessary to obtain more significant data on the sustainability of the prevention of recurrences covering the risk period.

Symptomatology (collected using EORTC QLQ-C30 and EORTC QLQ-LC13)

The symptomatology of the patients is assessed in the KEYNOTE 091 study with the EORTC QLQ-C30 and the disease-specific additional module EORTC QLQ-LC13.

The pharmaceutical company submitted evaluations based on the mean difference, which form the basis of the present assessment.

The EORTC QLQ-C30 showed a statistically significant difference to the disadvantage of pembrolizumab compared to the monitoring wait-and-see approach for the endpoint of appetite loss. However, it cannot be derived on the basis of the standardised mean difference that the observed effect is relevant.

There were no statistically significant differences between the treatment arms for the endpoints of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, constipation and diarrhoea.

In the disease-specific additional module EORTC QLQ-LC13, there was also no statistically significant difference between the treatment arms for all endpoints assessed.

Health status (assessed by EQ-5D VAS)

The health status is assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

The pharmaceutical company submitted evaluations based on the mean difference, which form the basis of the present assessment.

There were no signs of statistically significant differences between the treatment groups.

Overall, an advantage in the recurrence endpoint was observed for pembrolizumab in the morbidity endpoint category compared to the monitoring wait-and-see approach.

Quality of life

The quality of life of patients is assessed in the KEYNOTE 091 study using the functional scales of the EORTC QLQ-C30 questionnaire.

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The pharmaceutical company submitted evaluations based on the mean difference, which form the basis of the present assessment.

For the endpoint of social functioning, there was a statistically significant difference to the disadvantage of pembrolizumab versus the monitoring wait-and-see approach. However, it cannot be derived on the basis of the standardised mean difference that the observed effect is relevant.

There was no statistically significant difference between the treatment arms for the endpoints of global health status, physical functioning, role functioning, emotional functioning and cognitive functioning.

Overall, there was neither an advantage nor a disadvantage of pembrolizumab with regard to health-related quality of life.

Side effects

Adverse events in total

Adverse events (AEs) occurred in almost all patients. The results for the endpoint "total adverse events" are only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3), therapy discontinuation due to AEs

A statistically significant difference to the disadvantage of pembrolizumab over the monitoring wait-and-see approach was observed for each of the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs (CTCAE ≥ 3)

For the endpoints of immune-mediated SAEs and immune-mediated severe AEs, there was a statistically significant difference to the disadvantage of pembrolizumab versus the monitoring wait-and-see approach.

Endocrine disorders (SAEs), respiratory, thoracic and mediastinal disorders (SAEs), hepatobiliary disorders (severe AEs), infections and infestations (severe AEs)

For the specific AEs endocrine disorders (SAEs), respiratory, thoracic and mediastinal disorders (SAEs), hepatobiliary disorders (severe AEs), infections and infestations (severe AEs), there was a statistically significant difference to the disadvantage of pembrolizumab versus the monitoring wait-and-see approach, in detail.

In summary, a significant disadvantage was observed for pembrolizumab in the side effects endpoint category due to negative effects on SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. With regard to specific adverse events, there were disadvantages of pembrolizumab, in detail.

Overall assessment

The benefit assessment of pembrolizumab as monotherapy for the adjuvant treatment of adult patients with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy is based on the results of the KEYNOTE 091 study on the

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endpoint categories of mortality, morbidity, quality of life and side effects compared with the monitoring wait-and-see approach. The pharmaceutical company presented evaluations for the sub-population of patients with previous adjuvant chemotherapy in stages IB (T2a ≥ 4 cm) to IIIA (according to UICC 7th edition).

However, there were no statistically significant differences between the treatment groups for the overall survival.

Uncertainties remain regarding the subsequent therapies used after completion of the study medication.

The results on symptomatology, health status and health-related quality of life (assessed using the EORTC QLQ-C30, EORTC QLQ-LC13 and EQ 5D-VAS) indicate neither an advantage nor a disadvantage of pembrolizumab compared to the monitoring wait-and-see approach.

With regard to the results on recurrences, presented as recurrence rate and disease-free survival, an advantage of pembrolizumab compared to the monitoring wait-and-see approach was found. The avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting.

The results on side effects showed a significant disadvantage of pembrolizumab. This was based on statistically significant differences to the disadvantage of pembrolizumab in terms of the serious adverse events (AEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. In detail, there were disadvantages of pembrolizumab compared to the monitoring wait-and-see approach in terms of the specific AEs.

In the overall analysis, the advantage in the endpoint of recurrences was offset by significant disadvantages in terms of side effects.

As a result, no additional benefit was identified for pembrolizumab as a monotherapy for the adjuvant treatment of adult patients with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy compared with the monitoring wait-and-see approach.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient pembrolizumab.

The therapeutic indication assessed here is as follows:

"Keytruda as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy."

The G-BA determined the monitoring wait-and-see approach as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company presented the ongoing, triple-blinded phase III KEYNOTE 091 study comparing pembrolizumab with placebo.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms. Uncertainties remain with regard to subsequent therapies.

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No statistically significant difference between the treatment groups could be derived from the results on symptomatology, health status and health-related quality of life.

Considering the present curative therapeutic approach, the avoidance of recurrences represents a significant therapeutic goal. The results presented for the endpoints of recurrence rate and disease-free survival showed an advantage of pembrolizumab compared to the monitoring wait-and-see approach.

For side effects, there was a significant disadvantage of pembrolizumab due to statistically significant differences to the disadvantage of pembrolizumab in terms of serious adverse events (AEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. In detail, there were disadvantages of pembrolizumab compared to the monitoring wait-and-see approach in terms of the specific AEs.

In the overall analysis, the advantage in the endpoint of recurrences was offset by significant disadvantages in terms of side effects.

As a result, no additional benefit was identified for pembrolizumab as a monotherapy for the adjuvant treatment of adult patients with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy compared with the monitoring wait-and-see approach.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is primarily based on the information from the dossier of the pharmaceutical company. However, the figures provided on patient numbers were underestimated. The main reasons for this are the multiple withdrawal of patients with neoadjuvant therapy and an underestimated percentage of patients with adjuvant platinum-based chemotherapy. In order to enable a consistent consideration of the patient numbers, taking into account the resolutions made on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V, the relevant derivation steps of the resolutions on atezolizumab (resolution of 05.01.2023)[4] and on pembrolizumab (resolution of 17.10.2024)[5] are taken into account for the present calculation.

The incidence of lung carcinoma is based on the number of 60,076 patients forecast by the pharmaceutical company for 2024.

The following calculation steps are used to narrow down this patient group to the target population:

1. The percentage of patients with NSCLC is 73.6 to 83.6% (44,216 to 50,224).

[4] Benefit assessment procedure D-828 atezolizumab; www.g-ba.de/bewertungsverfahren/nutzenbewertung/849/
[5] Benefit assessment procedure D-1058 pembrolizumab; www.g-ba.de/bewertungsverfahren/nutzenbewertung/1082/

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2. The percentage of patients with NSCLC is subdivided by stage: IIA (1.87%), IIB (6.88%) to IIIA (11.31%) according to the UICC 8th edition[6]. It is assumed that the patients in stage IB (T= 4) according to UICC 8 covered by the therapeutic indication only make up a small number and are therefore not taken into account. This results in a range of 8,870 to 10,075.
3. The percentage of patients after tumour resection is 69.35% (573 to 651) in stage IIA, 66.98% (2,038 to 2,314) in stage IIB and 49.1% (2,456 to 2,790) in stage IIIA. Of these, 98.34% (564 to 641) in stage IIA, 98.34% (2,004 to 2,276) in stage IIB and 91.79% (2,255 to 2,561) in stage IIIA received a complete resection (4,822 to 5,478)[6].
4. Adjuvant chemotherapy was received by 63.1% to 66.2% (3,043 to 3,626) of resected patients.
5. Taking into account the percentage of SHI-insured patients of 88.3%, this results in 2,687 to 3,202 patients.

Due to uncertainties regarding the data basis in the target population in Germany, both an overestimation and an underestimation of patient numbers are possible.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Keytruda (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 12 September 2024):

https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with non-small cell lung carcinoma, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and other doctors from specialist groups participating in the Oncology Agreement.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on infusion-related reactions.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2024).

[6] German Cancer Society. Evaluation of key figures 2023 - annual report of the certified lung cancer study sites (audit year 2022 / year of key figures 2021). 2023

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The two pembrolizumab doses of 200 mg every 3 weeks or 400 mg every 6 weeks recommended according to the product information are listed in the cost representation.

The maximum treatment duration for adjuvant treatment with pembrolizumab is given as one year in the product information, but may be shorter on a patient-individual basis. Against this background, therefore, only the completed cycles in the treatment year are considered.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Treatment period:

Adults with non-small cell lung carcinoma at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17
	or			
	1 x per 42-day cycle	8.7	1	8
Appropriate comparator therapy				
Monitoring wait-and-see approach	Not calculable			

Consumption:

Adults with non-small cell lung carcinoma at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17	34 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8	32 x 100 mg

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adults with non-small cell lung carcinoma at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pembrolizumab 100 mg	1 CIS	€ 2,743.07	€ 2.00	€ 153.37	€ 2,587.70
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the

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prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services need to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence

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1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed

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therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

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In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with non-small cell lung carcinoma at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for pembrolizumab (Keytruda); Keytruda 25 mg/ml concentrate for the preparation of an infusion solution; last revised: August 2024

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 23 May 2023, the Pharmaceuticals Subcommittee determined the appropriate comparator therapy.

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A review of the appropriate comparator therapy took place once the positive opinion was granted. At its session on 7 November 2023, the Pharmaceuticals Subcommittee adjusted the appropriate comparator therapy.

On 19 April 2024, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 1 VerfO.

By letter dated 25 April 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 July 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2024. The deadline for submitting statements was 22 August 2024.

The oral hearing was held on 9 September 2024.

In order to prepare a recommendation for a resolution, the Pharmaceuticals Subcommittee commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 8 October 2024, and the proposed draft resolution was approved.

At its session on 17 October 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Pharmaceuticals Subcommittee	23 May 2023	Determination of the appropriate comparator therapy
Pharmaceuticals Subcommittee	7 November 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	3 September 2024	Information on written statements received; preparation of the oral hearing
Pharmaceuticals Subcommittee	9 September 2024	Conduct of the oral hearing
Working group Section 35a	17.09.2024; 30.09.2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Pharmaceuticals Subcommittee	8 October 2024	Concluding discussion of the draft resolution

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Plenum	17 October 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 17 October 2024

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

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