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 Cemiplimab (new therapeutic indication: non-small cell lung cancer, first-line)

of 20 January 2022

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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient cemiplimab (Libtayo) was listed for the first time on 1 August 2019 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 21 June 2021, cemiplimab received marketing authorisation for a new therapeutic indication to be 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 European 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, p. 7).

On 16 July 2021, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction

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with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient cemiplimab with the new therapeutic indication (monotherapy for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations. who have: patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or patients with metastatic NSCLC.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 November 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of cemiplimab compared to the appropriate comparator therapy could be determined on the basis of 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. 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 cemiplimab.

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:

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

2.1.1 Approved therapeutic indication of Cemiplimab (Libtayo) in accordance with the product information

LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation, or
- metastatic NSCLC.

Therapeutic indication of the resolution (resolution of 20 January 2022):

see new therapeutic indication according to marketing authorisation

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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2.1.2 Appropriate comparator therapy

Adults with locally advanced NSCLC, who are not candidates for definitive chemoradiation or have metastatic NSCLC, expressing PD-L1 in ≥ 50% of tumour cells with no EGFR, ALK or ROS1 aberrations; first-line treatment

Pembrolizumab

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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 Federal Joint Committee has already determined the patient-relevant advantage 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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to cemiplimab, medicinal products with the active ingredients cisplatin, docetaxel, gemcitabine, etoposide, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, vinorelbine, dabrafenib, trametinib, atezolizumab, bevacizumab, ipilimumab, nivolumab, and pembrolizumab are approved in the present therapeutic indication.

Medicinal products for the treatment of NSCLC with activating EGFR, ALK or ROS1 mutations were not considered here according to the intended therapeutic indication.

on 2. Non-medicinal treatments are unsuitable. For the patients covered by the present therapeutic indication, the determination of the appropriate comparator therapy was based on the assumption that there is neither an indication for definitive chemoradiation nor for definitive local therapy.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Atezolizumab: resolutions of 19.11.2021 and 02.04.2020
- Pembrolizumab: resolutions of 19.09.2019 and 03.08.2017
- Dabrafenib: resolution of 19.10.2017
- Trametinib: resolution of 19 .10.2017

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- Ipilimumab resolution of 03.06.2021
- Nivolumab: resolution of 03.06.2021

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (off-label use):

- carboplatin-containing medicinal products for advanced non-small cell lung cancer (NSCLC) - combination therapy

on 4. The generally accepted state of medical knowledge for the present indication was established using a systematic search for guidelines and reviews of clinical studies.

Of the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

The present therapeutic indication for first-line treatment includes both patients with metastatic NSCLC and patients with locally advanced NSCLC who are not candidates for definitive chemoradiation. In this regard, it was assumed that locoregional treatment measures were not an option when determining the appropriate comparator therapy.

For first-line treatment of metastatic, non-small cell lung cancer with PD-L1 expression in ≥ 50% of tumour cells, current guidelines recommend pembrolizumab monotherapy, regardless of histological status. The corresponding benefit assessment of pembrolizumab showed an indication of a considerable additional benefit compared to platinum-based chemotherapy (resolution of 3 August 2017). Pembrolizumab significantly improved overall survival, delayed the onset of significant disease symptoms and severe adverse events (CTCAE grade ≥ 3) and showed beneficial effects on health-related quality of life. In the written statements of the scientific-medical societies, pembrolizumab monotherapy is recommended as the appropriate comparator therapy, while the combination of an immune checkpoint inhibitor with chemotherapy is mentioned as a possible alternative.

Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy was assessed by the G-BA for the patient group with non-squamous NSCLC with a PD-L1 expression of ≥ 50% of the tumour cells or a TPS ≥ 50%, based on an adjusted indirect comparison versus pembrolizumab monotherapy by resolution of 19 September 2019. As the extent of the observed additional benefit in the endpoint of overall survival could not be quantified for the entire sub-population and an assessment of symptomatology and health-related quality of life was not possible, an additional benefit was determined, the extent of which is non-quantifiable. Based on these data, the combination therapy of pembrolizumab and platinum-containing chemotherapy is currently not considered an appropriate comparator therapy for the present patient population.

For squamous NSCLC, the combination of pembrolizumab plus carboplatin and either paclitaxel or nab-paclitaxel is also approved for first-line therapy. For patients with PD-L1 expression ≥ 50% of the tumour cells or a TPS ≥ 50%, no additional benefit over pembrolizumab monotherapy was identified by the G-BA in its resolution of 19 September 2019, as no suitable data were available for comparison with the appropriate comparator therapy. This combination therapy is therefore not considered an appropriate comparator therapy for the present patient population.

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In addition, for non-squamous metastatic NSCLC, atezolizumab in combination with bevacizumab, paclitaxel and carboplatin is approved for first-line therapy. For patients with PD-L1 expression ≥ 50% of the tumour cells or a TPS ≥ 50%, no additional benefit was identified by the G-BA in its resolution of 2 April 2020, as no data were available for comparison with the appropriate comparator therapy. Atezolizumab is also approved in combination with nab-paclitaxel and carboplatin for the first-line therapy of non-squamous NSCLC. For patients with PD-L1 expression ≥ 50% of the tumour cells or a TPS ≥ 50%, no additional benefit was identified by the G-BA in its resolution of 2 April 2020, as no data were available for comparison with the appropriate comparator therapy. Therefore, these two combination therapies are not found to be appropriate comparator therapy for the present patient group.

Another combination therapy approved for the first-line treatment of metastatic NSCLC is nivolumab in combination with ipilimumab and two cycles of platinum-based chemotherapy. Data for this combination therapy, compared to the appropriate comparator therapy, were also not available for the present patient group with a PD-L1 expression of ≥ 50 % of the tumour cells or a TPS ≥ 50%. Therefore, no additional benefit could be determined by the G-BA resolution of 3 June 2021. Nivolumab in combination with ipilimumab and two cycles of platinum-based chemotherapy is therefore not considered an appropriate comparator therapy for the present patient group.

Furthermore, atezolizumab as monotherapy is also available for first-line treatment. With the resolution of 19 November 2021, the G-BA determined an additional benefit as not proven for the patient group with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% of the tumour cells on the basis of an indirect comparison with pembrolizumab. Atezolizumab as monotherapy is not considered an appropriate comparator therapy for the present patient group.

In the overall assessment, monotherapy with pembrolizumab is determined to be the only appropriate comparator therapy.

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

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2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

Justification:

To demonstrate an additional benefit of cemiplimab as monotherapy compared to the appropriate comparator therapy, the pharmaceutical company presents three independently calculated, adjusted indirect comparisons in the dossier: on the side of cemiplimab, the randomised controlled trial R2810-ONC-1624 and on the side of the appropriate comparator therapy with pembrolizumab as monotherapy, the KEYNOTE 024 and KEYNOTE 042 studies (separately for squamous and non-squamous histology). The bridge comparator for the indirect comparisons presented was "platinum-based combination chemotherapy".

R2810-ONC-1624 study

The R2810-ONC-1624 study is an ongoing, open-label RCT comparing cemiplimab with a platinum-based combination chemotherapy.

A total of 710 adult patients with confirmed stage IIIB, IIIC or IV NSCLC without EGFR mutation, ALK translocation or ROS1 translocation whose tumours had PD-L1 expression ≥ 50% were enrolled in the study. Patients were not allowed to have received previous systemic therapy for the advanced or metastatic stage. In addition, definitive chemoradiation was not allowed to be suitable for the patients.

Patients were allocated in a 1:1 ratio to either treatment with cemiplimab (N = 356) or platinum-based combination chemotherapy (N = 354). The following options were used as platinum-based combination therapy: pemetrexed + cisplatin, pemetrexed + carboplatin, paclitaxel + cisplatin, paclitaxel + carboplatin, gemcitabine + cisplatin or gemcitabine + carboplatin. The combination with pemetrexed was only considered for patients with non-squamous histology. The platinum component for chemotherapy was used for a maximum of 4 to 6 cycles in the R2810-ONC-1624 study. After at least 4 cycles, maintenance treatment with pemetrexed was possible for patients with non-squamous histology.

Prior to August 2018, PD-L1 expression testing was not performed according to the 22C3 assay instructions. The pharmaceutical company presents results of a sub-population comprising the patients enrolled before August 2018 in whom PD-L1 expression of the tumours of ≥ 50% was verified in a retest, as well as the patients enrolled from August 2018 onwards. This sub-population comprises 283 patients in the intervention arm and 280 patients in the comparator arm and is relevant for the benefit assessment.

Treatment was given until disease progression, unacceptable toxicity, death or withdrawal of consent.

After disease progression and confirmed suitability, patients in the intervention arm could be treated for a further 108 weeks with cemiplimab in combination with platinum-based combination chemotherapy (4 cycles). Patients in the comparator arm were able to switch to treatment with cemiplimab as monotherapy (up to 108 weeks). It should be noted that cemiplimab is not approved for treatment after prior chemotherapy.

The study was conducted in 138 study sites across Australia, Asia, Europe, Central and South America. Primary endpoints in the study were overall survival and progression-free survival (PFS). Patient-relevant secondary endpoints were morbidity, health-related quality of life, and

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adverse events (AEs). The pharmaceutical company presents the results of the sub-population only for the endpoints of the categories mortality, morbidity and health-related quality of life. For the side effects, the pharmaceutical company uses the results of the overall safety population (697 patients).

There are data cut-offs from 27.09.2019 (1st interim analysis) and from 01.03.2020 (2nd interim analysis). Due to the superiority of cemiplimab over platinum-based combination chemotherapy in terms of overall survival, the final analysis was performed at the time of the data cut-off of the 2nd interim analysis (01.03.2020). For the present benefit assessment, the data cut-off from 01.03.2020 is used. This second data cut-off was prospectively planned after reaching 238 events for the overall survival endpoint.

KEYNOTE 024 study

The KEYNOTE 024 study is an open-label RCT comparing pembrolizumab with platinum-based combination chemotherapy. Adult patients with confirmed metastatic NSCLC without EGFR mutation or ALK translocation whose tumours had PD-L1 expression ≥ 50% were enrolled in the study. Prior systemic, antineoplastic therapy for the metastatic stage was not allowed.

A total of 305 patients were enrolled in the KEYNOTE 024 study and randomised in a 1:1 ratio to either treatment with pembrolizumab monotherapy (N = 154) or platinum-based combination chemotherapy (N = 151). The following treatment options were available as platinum-based combination therapy: pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin or paclitaxel + carboplatin, whereby the combination with pemetrexed was only considered for patients with non-squamous histology. The platinum component for chemotherapy was used for a maximum of 4 to 6 cycles in the KEYNOTE 024 study. Thereafter, maintenance treatment with pemetrexed was possible and recommended for the patients with non-squamous epithelial histology.

Patients were treated until disease progression, the occurrence of unacceptable side effects or study discontinuation due to the decision of the principal investigator or the patient.

The study, conducted in 142 centres across Oceania, Europe, Asia and North America, was completed in 2016. The primary endpoint of the study was progression-free survival (PFS). Patient-relevant secondary endpoints were overall survival, morbidity endpoints, health-related quality of life and AEs.

KEYNOTE 042 study

The KEYNOTE 042 study is an ongoing, open RCT. The study compared pembrolizumab with a combination of carboplatin and either paclitaxel or pemetrexed. Adults with confirmed diagnosis of an NSCLC whose tumours expressed PD-L1 ≥ 1% and were in locally advanced or metastatic stage were enrolled in the study. Previous systemic therapy was not allowed in the study.

A total of 1,274 patients were randomised in a 1:1 ratio to the intervention arm (637 patients) or the comparator arm (637 patients). The treatment options in the comparator arm of the study were as follows: pemetrexed + carboplatin or paclitaxel + carboplatin, whereby the combination with pemetrexed was only considered for patients with non-squamous histology. Carboplatin was used in the KEYNOTE 042 study in patients with non-squamous histology for a maximum of 4 to 6 cycles. After at least 4 cycles, maintenance treatment with pemetrexed was possible and recommended for patients with non-squamous histology.

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Patients with a PD-L1 expression ≥ 50% (599 patients) are relevant for the benefit assessment. Published data[2] are available for the entire relevant sub-population for the overall survival endpoint. Further analyses are available from the past benefit assessment procedures, but limited to those patients for whom carboplatin was a suitable therapy option according to the requirements of the AM-RL for off-label use (Annex VI to Section K). These analyses are only available separately for 176 patients with squamous and 120 patients with non-squamous histology and comprise just under 50% of the relevant sub-population.

Patients were treated until disease progression, complete response, occurrence of unacceptable side effects or study discontinuation based on the decision of the principal investigator or the patients.

The ongoing study is being conducted in 196 centres across South America, Europe, Asia, South Africa and Canada. The primary endpoint of the study was overall survival. Patient-relevant secondary endpoints were AEs.

Assessment of the suitability of the indirect comparisons

The pharmaceutical company presents data from independently calculated, adjusted indirect comparisons with the R2810-ONC-1624 and KEYNOTE 024 studies or R2810-ONC-1624 and KEYNOTE 042 studies (separately for squamous and non-squamous histology). A meta-analytic summary of the results on the pembrolizumab side and a subsequent indirect comparison with the R2810-ONC-1624 study was not performed by the pharmaceutical company. This approach was criticised by IQWiG in the dossier assessment and a meta-analytic summary of the KEYNOTE 024 and KEYNOTE 042 studies with subsequent indirect comparison with the R2810-ONC-1624 study was described as necessary. However, in the written statement procedure, neither corresponding evaluations were submitted by the pharmaceutical company nor, in the view of the G-BA, comprehensible reasons for waiving this were presented.

The methodological approach on which this assessment is based is therefore assessed by the G-BA as inappropriate. In the view of the G-BA, a meta-analytic summary of the KEYNOTE 024 and KEYNOTE 042 studies with subsequent indirect comparison with the R2810-ONC-1624 study would have increased the statistical power and also allowed further statements on the heterogeneity between the studies.

Furthermore, the similarity of the studies cannot be assessed with sufficient certainty:

With regard to the bridge comparator "platinum-based combination chemotherapy", there are differences in the selection and percentage of both the platinum component and the concomitant active ingredient used between the R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042 studies.

Based on the post hoc restricted analysis of the KEYNOTE 042 study, the patients, for whom, according to a retrospective survey, carboplatin was a suitable therapy option in accordance with the AM-RL guidelines on off-label use (Annex VI to Section K), only received carboplatin in the comparator arm. However, these restrictions were not made in the KEYNOTE 024 and

[2] Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial; Mok et al; Lancet 2019 May 4;393(10183):1819-1830.

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R2810-ONC-1624 studies and both cisplatin and carboplatin were available in the comparator arm.

The three studies used by the pharmaceutical company also differ with regard to the chemotherapy component used as a concomitant active ingredient with the platinum component. Thus, paclitaxel in combination with cisplatin was a treatment option only in the R2810-ONC-1624 study. In the KEYNOTE 024 and 042 studies, patients received paclitaxel exclusively in combination with carboplatin. Furthermore, patients in the comparator arm of the R2810-ONC-1624 and KEYNOTE 024 studies but not in the KEYNOTE 042 study could be treated with gemcitabine. There are also differences or no concrete data are available for the percentages of patients in the studies used by the pharmaceutical company who were treated with the respective chemotherapeutic agents. This also relates to the percentages of patients in the respective studies who received maintenance treatment with pemetrexed.

Overall, the similarity of the bridge comparators between the studies is therefore judged to be not reliably assessable.

Also with regard to treatment and duration of observation as well as subsequent therapies, the similarity between the studies cannot be conclusively assessed because the data for the KEYNOTE 042 study are neither available for treatment and duration of observation nor for specific subsequent therapies, in contrast to the R2810-ONC-1624 and KEYNOTE 024 studies.

As a result, the submitted adjusted indirect comparisons are not assessed as suitable for the assessment of the additional benefit of cemiplimab compared to the appropriate comparator therapy, in particular due to the criticism of the methodological approach outlined above.

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Overall assessment / conclusion

For the benefit assessment of cemiplimab as monotherapy for the first-line treatment of adult patients with locally advanced, non-small cell lung cancer (NSCLC), who are not candidates for definitive chemoradiation, or metastatic (NSCLC), whose tumours express PD-L1 in ≥ 50% of tumour cells and do not have EGFR, ALK or ROS1 aberrations, data are available from three independently calculated, adjusted indirect comparisons: on the side of cemiplimab, the randomised controlled trial R2810-ONC-1624 and on the side of the appropriate comparator therapy with pembrolizumab as monotherapy, the KEYNOTE 024 and/or KEYNOTE 042 studies (separately for squamous and non-squamous histology). The bridge comparator for the indirect comparisons presented was "platinum-based combination chemotherapy".

The adjusted indirect comparisons submitted by the pharmaceutical company are not considered suitable overall for the present assessment. In this respect, the main point of criticism is the methodological procedure, as no meta-analytic summary of the KEYNOTE 024 and 042 studies with a subsequent indirect comparison with the R2810-ONC-1624 study was carried out by the pharmaceutical company. This approach is not considered appropriate by the G-BA.

Furthermore, the similarity between the studies cannot be assessed with sufficient certainty. Thus, with regard to the bridge comparator "platinum-based chemotherapy", there are differences in the selection and percentage of both the platinum component used and the concomitant active ingredient. In addition, there is a lack of information on the treatment duration, the duration of observation as well as on subsequent therapies.

Overall, there are therefore no suitable data for the assessment of the additional benefit of cemiplimab compared with the appropriate comparator therapy. An additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of cemiplimab as monotherapy. The therapeutic indication assessed here is as follows:

LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation, or
- metastatic NSCLC.

Pembrolizumab was determined to be the appropriate comparator therapy.

Data are available from three independently calculated, adjusted indirect comparisons: on the side of cemiplimab, the randomised controlled trial R2810-ONC-1624, and on the side of the appropriate comparator therapy with pembrolizumab as monotherapy, the KEYNOTE 024 and KEYNOTE 042 studies (separated according to squamous and non-squamous histology). The bridge comparator for the indirect comparisons presented was "platinum-based combination chemotherapy".

The adjusted indirect comparisons submitted by the pharmaceutical company are not considered suitable overall for the present assessment. In this respect, the main point of criticism is the methodological procedure, as no meta-analytic summary of the KEYNOTE 024 and 042 studies with a subsequent indirect comparison with the R2810-ONC-1624 study was

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carried out by the pharmaceutical company. This approach is not considered appropriate by the G-BA.

Furthermore, the similarity between the studies cannot be assessed with sufficient certainty. Thus, with regard to the bridge comparator "platinum-based chemotherapy", there are differences in the selection and percentage of both the platinum component used and the concomitant active ingredient. In addition, there is a lack of information on the treatment duration, the duration of observation as well as on subsequent therapies.

Overall, there are therefore no suitable data for the assessment of the additional benefit of cemiplimab compared with the appropriate comparator therapy. An additional benefit is not proven.

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).

In order to allow consistent consideration of 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 in the therapeutic indication of non-small cell lung cancer, the incidence of 62,380 patients forecast by the Robert Koch Institute for 2020 is used for the present calculation. This differs from the incidence of 63,746 patients forecast by the pharmaceutical company for 2021.

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

1. The percentage of lung cancer patients with NSCLC is 80.3 - 82% (50,091 - 51,152 patients).
2. Of these, 53.6 - 57.6% of patients are in stage IIIB/IV (26,849 - 29,463 patients)
3. First-line therapy is given in 76.9 - 78.5% of cases (20,647 - 23,129 patients).
4. The percentage of patients without EGFR mutation is 85.8 - 89.7%[3][4]. The percentage of patients without ALK translocation is 94.9 - 98.0%[4]. The percentage of patients without ROS translocation is 96.3 - 98.5%. In total, the number is 16,189 - 20,027 patients without EGFR mutation or ALK translocation and without ROS translocation.
5. The percentage of patients with PD-L1 high-expressing tumours (PD-L1 expression ≥ 50% of the tumour cells) is 28.9% (4,679 - 5,788 patients).
6. Taking into account a percentage of patients insured by the SHI of 88.3%, this results in 4,131 - 5,111 patients with a PD-L1 expression ≥ 50%

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

[3] Benefit assessment according to Section 35a SGB V, A21-86, osimertinib (NSCLC, adjuvant), 29.09.2021
[4] Benefit assessment according to Section 35a SGB V, A21-98, cemiplimab (non-small cell lung cancer), 28.10.2021

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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 Libtayo (active ingredient: cemiplimab) at the following publicly accessible link (last access: 25 November 2021):

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

Treatment with cemiplimab may only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of adult patients with non-small cell lung cancer, 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.

Patients are to be selected for treatment with cemiplimab as monotherapy on the basis of PD-L1 tumour expression, confirmed by a validated test.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on cemiplimab:

− information brochure for patients

− patient pass

The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with cemiplimab as well as on infusion-related reactions.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2022).

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

The recommended dosage for pembrolizumab in monotherapy is 200 mg every 3 weeks or 400 mg every 6 weeks. Both therapy regimens are used for the cost calculation.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number

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of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The annual treatment costs shown refer to the first year of treatment.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Cemiplimab	1 x per 21-day cycle	17.4 cycles	1	17.4
Appropriate comparator therapy				
Adults with locally advanced NSCLC, who are not candidates for definitive chemoradiation or have metastatic NSCLC, expressing PD-L1 in ≥ 50% of tumour cells with no EGFR, ALK or ROS1 aberrations; first-line treatment				
Pembrolizumab	1 x per 21-day cycle	17.4 cycles	1	17.4
	or			
	1 x per 42-day cycle	8.7 cycles	1	8.1

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Consumption:

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

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					
Cemiplimab	350 mg	350 mg	1 x 350 mg	17.4	17.4 x 350 mg
Appropriate comparator therapy					
Adults with locally advanced NSCLC, who are not candidates for definitive chemoradiation or have metastatic NSCLC, expressing PD-L1 in ≥ 50% of tumour cells with no EGFR, ALK or ROS1 aberrations; first-line treatment					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg

Costs:

Costs of the medicinal products:

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 usage. 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.

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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					
Cemiplimab	1 CIS	€ 4,549.10	€ 1.77	€ 256.51	€ 4,290.82
Appropriate comparator therapy					
Pembrolizumab	1 CIS	€ 3,037.30	€ 1.77	€ 170.17	€ 2,865.36
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 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 had 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 01.10.2009 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 drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 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.

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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 6 October 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 16 July 2021 the pharmaceutical company submitted a dossier for the benefit assessment of cemiplimab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 21 July 2021 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 cemiplimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 October 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 November 2021. The deadline for submitting written statements was 22 November 2021.

The oral hearing was held on 6 December 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products 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 11 January 2022, and the proposed resolution was approved.

At its session on 20 January 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

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Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	06 October 2020	Implementation of the appropriate comparator therapy
Working group Section 35a	01 December 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	06 December 2021	Conduct of the oral hearing
Working group Section 35a	15 December 2021 05 January 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	11 January 2022	Concluding discussion of the draft resolution
Plenum	20 January 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 January 2022

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

Prof. Hecken

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