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, PD-L1 expression ≥ 1%, combination with platinum-based chemotherapy)

of 19 October 2023

Contents

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 is 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 24 March 2023, 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 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 20 April 2023, 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 1, number 2 of the Rules of

Procedure (VerfO) of the G-BA on the active ingredient cemiplimab with the new therapeutic indication.

"LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

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

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The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 August 2023 on the G-BA website (www.g-ba.de), 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 in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of 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 19.10.2023):

see the approved therapeutic indication

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

Appropriate comparator therapy for cemiplimab in combination with platinum-based chemotherapy:

- pembrolizumab as monotherapy

or

- atezolizumab as monotherapy

or

- cemiplimab as monotherapy

or

- nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0-1)

or

- pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0-1 and a squamous NSCLC)

or

- pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients without ECOG-PS 0-1 and a non-squamous NSCLC)

or

- atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0-1 and a non-squamous NSCLC)

or

- atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0-1 and a non-squamous NSCLC)

b) Adults with locally advanced or metastatic NSCLC expressing PD-L1- (in ≥ 1% to < 50% of tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

Appropriate comparator therapy for cemiplimab in combination with platinum-based chemotherapy:

- pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients without ECOG PS 0-1 and a non-squamous NSCLC)

or

- pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0-1 and a squamous NSCLC)

or

- atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells)

or

- atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0-1 and a non-squamous NSCLC)

or

- atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0-1 and a non-squamous NSCLC)

or

- nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0-1)

or

- carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) cf. Annex VI to Section K of the Pharmaceuticals Directive (only for patients with ECOG PS 2)

or

- carboplatin in combination with nab-paclitaxel (only for patients with ECOG PS 2)

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 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 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.

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

on 1. In the present therapeutic indication, it is assumed that patients will not be eligible for molecularly stratified therapy (directed against BRAF, KRAS G12C, METex14 or RET) at the time of therapy with cemiplimab in combination with platinum-based chemotherapy. Molecularly stratified therapy for EGFR, ALK or ROS1 aberrations is already excluded by the therapeutic indication.

With regard to the authorisation status for first-line treatment of locally advanced or metastatic NSCLC with no EGFR, ALK or ROS1 aberrations, the cytostatic agents cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, vinorelbine and the antibodies atezolizumab, bevacizumab, cemiplimab, durvalumab, ipilimumab, nivolumab, pembrolizumab and tremelimumab are available in general in addition to cemiplimab in combination with platinum-based chemotherapy.

on 2. For the present therapeutic indication, it is assumed that there is neither an indication for definitive chemoradiotherapy nor for definitive local therapy. Therefore, a non-medicinal treatment cannot be considered in the present therapeutic indication.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:
- durvalumab (NSCLC, first-line; resolution of 5 October 2023)
- tremelimumab (NSCLC, first-line; resolution of 5 October 2023)
- cemiplimab (NSCLC, first-line; resolution of 20 January 2022)
- atezolizumab (NSCLC, first-line; resolutions of 2 April 2020 and 19 November 2021)
- ipilimumab (NSCLC, first-line; resolution of 3 June 2021)
- nivolumab (NSCLC, first-line; resolution of 3 June 2021)
- pembrolizumab (NSCLC, first-line; resolutions of 3 August 2017 and 19 September 2019)

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 recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as 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"). A written statement by the AkdÄ and a joint written statement by the Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V. (German Society for Haematology and Medical Oncology), the Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e. V. (German Respiratory Society), the Arbeitsgemeinschaft Thorakale Onkologiein the Arbeitsgemeinschaft Internistische Onkologie in der Deutschen Krebsgesellschaft e.V. (Working Group for Thoracic Oncology of the Working Group for Internal Oncology of the German Cancer Society) and the Pneumologisch-Onkologische Arbeitsgemeinschaft

der Deutschen Krebsgesellschaft e. V. (Working Group for Pneumological Oncology of the German Cancer Society) are available from other procedures.

Among 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.

According to the present therapeutic indication, cemiplimab in combination with platinum-based chemotherapy is indicated for patients in the locally advanced stage, who are not candidates for definitive chemoradiation. For the determination of the appropriate comparator therapy, it is also assumed that there is no indication of a definitive local therapy, which means that a palliative treatment setting can be assumed overall. For patients in this advanced disease and treatment setting, the same treatment recommendations apply as for the metastatic stage. With regard to the determination of the appropriate comparator therapy in first-line treatment, the G-BA differentiates into two sub-populations with a cut-off value of PD-L1 expression of 50% on tumour cells based on the available evidence on therapy options depending on PD-L1 expression:

a) Adults with locally advanced or metastatic NSCLC expressing PD-L1- (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

For first-line treatment of NSCLC with PD-L1 expression in ≥ 50% of tumour cells, current guidelines recommend monotherapy with the immune checkpoint inhibitors (ICI) atezolizumab, cemiplimab and pembrolizumab, regardless of histological status.

The current written statements of the AkdÄ and the scientific-medical societies also name monotherapy with an ICI as the treatment standard concerning the question of comparator therapy from other procedures. This is based on significant improvements in overall survival and progression-free survival with fewer side effects and better quality of life compared to chemotherapy. The AkdÄ additionally refers to the medical treatment practice where the therapy with ICI has become established.

In the written statement of the scientific-medical societies, the combination therapies of an ICI and a platinum-containing chemotherapy are regarded as an alternative to ICI monotherapies, especially for patients with remission pressure due to burdensome symptomatology, high tumour burden or rapid tumour growth. Current guidelines also recommend combination therapies consisting of an ICI and chemotherapy. In terms of therapy selection, a distinction is made between patients with a reduced general condition (ECOG performance status (PS) 2) and patients with a good general condition (ECOG-PS 0-1). Current guidelines refer to the limited data basis available for the treatment of patients with ECOG-PS 2. Accordingly, current guidelines recommend combination therapies consisting of an ICI and chemotherapy for patients with ECOG-PS 0-1. It is also clear from the written statement of the AkdÄ that the treatment selection is influenced by additional parameters. These include, in particular, the general condition and comorbidity.

For patients with squamous NSCLC, the combination therapy of pembrolizumab, carboplatin and either paclitaxel or nab-paclitaxel is available. For patients with non-squamous NSCLC, pembrolizumab can be used in combination with pemetrexed and platinum-containing chemotherapy, atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, or atezolizumab in combination with nab-paclitaxel and

carboplatin. The combination therapies of nivolumab and ipilimumab and two cycles of platinum-based chemotherapy as well as durvalumab in combination with tremelimumab are also available as treatment options regardless of histology. The active ingredients durvalumab and tremelimumab concern a new treatment option in the present therapeutic indication. The active ingredients were only recently approved (marketing authorisation on 30 January 2023). Based on the generally accepted state of medical knowledge, durvalumab in combination with tremelimumab is not determined to be an appropriate comparator therapy for the present resolution.

In the overall assessment, based on the current body of evidence for this patient group, the G-BA approved pembrolizumab, atezolizumab and cemiplimab as monotherapy and the combination therapies nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1), pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0-1 and squamous NSCLC), pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG-PS 0-1 and non-squamous NSCLC), atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG-PS 0-1 and non-squamous NSCLC) as well as atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0-1 and non-squamous NSCLC) as equally appropriate comparator therapies. The appropriate comparator therapy determined here includes several therapy options. In this context, individual therapy options only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

b) <u>Adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 1% to < 50% of tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy</u>

For first-line treatment of NSCLC with PD-L1 expression in < 50% of the tumour cells, the current guidelines also make the therapy recommendations depending on ECOG-PS and tumour histology.

For patients with an ECOG-PS of 0-1, current guidelines recommend the combination therapies of the ICIs atezolizumab, nivolumab or pembrolizumab and chemotherapy, depending on the tumour histology. This is supported by the written statements of the scientific-medical societies, which point to the survival advantage of these therapy options over chemotherapy alone.

For patients with squamous NSCLC, the combination therapy of pembrolizumab, carboplatin and either paclitaxel or nab-paclitaxel is available. For patients with non-squamous NSCLC, pembrolizumab can be used in combination with pemetrexed and platinum-containing chemotherapy, atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, or atezolizumab in combination with nab-paclitaxel and carboplatin. The combination therapies of nivolumab and ipilimumab and two cycles of platinum-based chemotherapy as well as durvalumab in combination with tremelimumab are also available as treatment options regardless of histology. The active ingredients durvalumab and tremelimumab concern a new treatment option in the present therapeutic indication. The active ingredients were only recently approved (marketing authorisation on 30 January 2023). Based on the generally accepted state

of medical knowledge, durvalumab in combination with tremelimumab is not determined to be an appropriate comparator therapy for the present resolution.

Furthermore, the ICI atezolizumab is available as monotherapy, which, in contrast to the other ICIs, is also indicated in monotherapy with a PD-L1 expression of < 50%. Specifically, atezolizumab is approved as monotherapy from a PD-L1 expression ≥ 10% in tumour-infiltrating immune cells. Current guidelines recommend monotherapy with atezolizumab according to the marketing authorisation and regardless of the ECOG-PS.

For patients with an ECOG-PS 2, chemotherapy can also be a relevant therapy option according to the current guidelines. According to the current written statements of the scientific-medical societies on the question of comparator therapy from other procedures, combination chemotherapy with two cytostatic agents is more effective than monochemotherapy. In addition, it is stated that although significantly higher remission rates are achieved with cisplatin than with carboplatin, these differences have not been shown in combinations with third-generation medicinal products. In terms of overall survival, the two platinum derivatives are described by the scientific-medical societies as having an equivalent effect. The choice of the platinum active ingredient among the corresponding platinum-containing chemotherapies is primarily based on the specific toxicity expected, with cisplatin having a higher toxicity. Taking into account the relevance of toxicity, particularly for patients with a reduced general condition (ECOG-PS 2), the G-BA considers it appropriate to designate carboplatin alone as the platinum active ingredient for patients with an ECOG-PS 2, thereby determining carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) as the appropriate comparator therapy. The combination of carboplatin and nab-paclitaxel is also recommended and determined to be an appropriate comparator therapy for patients with an ECOG-PS 2. In contrast to cisplatin, carboplatin is not approved for the treatment of NSCLC, but can be prescribed for patients as "off-label use" (see Annex VI to Section K of the Pharmaceuticals Directive).

Taking into account the current body of evidence, the G-BA has approved atezolizumab as monotherapy for patients with PD-L1 expression < 50% (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells) as well as the combination therapies of pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG-PS 0-1 and non-squamous NSCLC), pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0-1 and squamous NSCLC), atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG-PS 0-1 and non-squamous NSCLC), atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0-1 and non-squamous NSCLC); nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1), carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) cf. Annex VI to Section K of the Pharmaceuticals Directive (only for patients with ECOG-PS 2), carboplatin in combination with nab-paclitaxel (only for patients with ECOG-PS 2) as equally appropriate comparator therapies. The appropriate comparator therapy determined here includes several therapy options. In this context, the therapy options only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

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

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 cemiplimab is assessed as follows:

a) Adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

An additional benefit is not proven.

Justification:

In the absence of direct comparator studies of cemiplimab in combination with platinum-based chemotherapy versus the appropriate comparator therapy, the pharmaceutical company uses two adjusted indirect comparisons according to the procedure of Bucher et al. for the proof of an additional benefit. For the adjusted indirect comparisons versus pembrolizumab as monotherapy via the bridge comparator of platinum-based chemotherapy, the pharmaceutical company includes the EMPOWER-Lung 3 study on the side of cemiplimab in combination with platinum-based chemotherapy and the KEYNOTE 024 and KEYNOTE 042 studies on the side of pembrolizumab as monotherapy.

Description of the EMPOWER-Lung 3 study

The EMPOWER-Lung 3 study is an ongoing, double-blind, randomised, controlled phase III study comparing cemiplimab + platinum-based chemotherapy with placebo + platinum-based chemotherapy, being conducted in 74 study sites in Europe as well as Asia.

Adults with histologically or cytologically confirmed locally advanced NSCLC (stage IIIB and IIIC) or metastatic NSCLC with no EGFR mutation, ALK translocation or ROS1 fusion were enrolled. Patients should be in a good general condition (corresponding to ECOG-PS ≤ 1). Patients in stage IIIB and IIIC were not allowed to be candidates for definitive chemoradiation, and patients in stage IV were not allowed to have received prior systemic therapy for the advanced or metastatic stage.

The EMPOWER-Lung 3 study enrolled 466 patients and allocated them in a 2:1 ratio to treatment with either cemiplimab + platinum-based chemotherapy (N = 312) or placebo + platinum-based chemotherapy (N = 154), stratified by histology (squamous, non-squamous) and PD-L1 expression (in < 1%, 1 - 49%, ≥ 50%). The treatment options in platinum-based chemotherapy were pemetrexed + cisplatin, pemetrexed + carboplatin, paclitaxel + cisplatin or paclitaxel + carboplatin. Therapy with pemetrexed was only considered for patients with non-squamous histology.

The choice of platinum-based chemotherapy was made by the principal investigator prior to randomisation according to regional guidelines or standard of care.

The administration of the study medication was carried out according to the requirements in the product information.

Patients were treated until disease progression, occurrence of unacceptable side effects, commencement of a antineoplastic subsequent therapy or study discontinuation.

The primary endpoint of the study is overall survival. Patient-relevant secondary endpoints are endpoints on morbidity, health-related quality of life and AEs.

For the EMPOWER-Lung 3 study, 3 data cut-offs are available in total:

- 1st data cut-off of 03.01.2021: 1st pre-specified interim analysis planned after the occurrence of 146 (50%) deaths in the total study population
- 2nd data cut-off of 14.06.2021: 2nd pre-specified interim analysis (primary analysis) planned after the occurrence of 204 (70%) deaths in the total study population
- 3rd data cut-off of 14.06.2022: data cut-off carried out post hoc; the analyses were updated to the EMA-approved therapeutic indication (patients expressing PD-L1 (in ≥ 1% of the tumour cells)); the results of this data cut-off are presented in the EPAR

For the benefit assessment, analyses of 2 sub-populations of the EMPOWER-Lung 3 study are submitted by the pharmaceutical company at the data cut-off of 14.06.2022. These include patients with non-squamous histology, PD-L1 expression ≥ 50% and a chemotherapy regimen consisting of pemetrexed + carboplatin or cisplatin (48 vs 21 in the intervention and comparator arms, respectively). Secondly, analyses for patients with squamous histology, PD-L1 expression ≥ 50% and a chemotherapy regimen consisting of paclitaxel + carboplatin (35 vs 21 in the intervention and comparator arms, respectively).

Description of the KEYNOTE 024 study

The KEYNOTE 024 study is an open-label, randomised, controlled phase III study comparing pembrolizumab with platinum-based combination chemotherapy, conducted from 2014 to 2016 in 142 study sites in North America, Europe and Australia/ New Zealand.

Adults with histologically or cytologically confirmed metastatic NSCLC with no EGFR mutation or ALK translocation whose tumours showed a PD-L1 expression ≥ 50% were enrolled. Patients should be in a good general condition (corresponding to ECOG-PS ≤ 1). Prior systemic, antineoplastic therapy for the metastatic stage was not allowed.

In total, 305 patients were randomised in a 1:1 ratio to treatment with pembrolizumab monotherapy (N = 154) or to one of 5 possible treatment options as platinum-based combination chemotherapy (N = 151), stratified by histology (squamous, non- squamous), geographic region (East Asia, non-East Asia) and ECOG-PS (0 vs 1). The treatment options were: 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 principal investigator made a patient-individual selection of the combination chemotherapy prior to randomisation.

The study medication was administered according to the requirements in the product information or the Pharmaceuticals Directive (AM-RL) for off-label use (Annex VI to Section K). 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 for the patients with non-squamous histology.

Patients were treated until disease progression, occurrence of unacceptable side effects or study discontinuation.

The primary endpoint of the study was PFS. Patient-relevant secondary endpoints were overall survival, morbidity endpoints, health-related quality of life and AEs.

The pharmaceutical company uses the results of a sub-population for the data cut-off of the 2nd interim analysis of 09.05.2016 for the adjusted indirect comparison.

The sub-population of KEYNOTE 024 submitted by the pharmaceutical company for the benefit assessment comprises patients with non-squamous epithelial histology, PD-L1 expression ≥ 50% and a chemotherapy regimen consisting of carboplatin + pemetrexed or cisplatin + pemetrexed. The pharmaceutical company uses available analyses from the benefit assessment procedure 2019-04-01-D-447 for this sub-population.

Description of the KEYNOTE 042 study

The KEYNOTE 042 study is an open-label, randomised, controlled phase III study comparing pembrolizumab versus a combination of carboplatin and either paclitaxel or pemetrexed, conducted from 2014 to 2022 in 196 study sites in North and South America, Asia and Eastern Europe.

Adults with histologically or cytologically 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. The ECOG-PS should be 0 or 1 in the enrolled patients.

In total, 1,274 patients were randomised in a 1:1 ratio to the intervention arm (pembrolizumab: N = 637) or the comparator arm (N = 637), randomised by ECOG-PS (0, 1), histology (squamous vs non-squamous), PD-L1 expression (≥ 50% vs 1 to 49%) and geographic region (East Asia vs non-East Asia).

The medical investigators made a patient-individual selection of the treatment option in the comparator arm (pemetrexed + carboplatin or paclitaxel + carboplatin) prior to randomisation, with the combination with pemetrexed only being considered for patients with non-squamous histology.

The treatment with the study medication was carried out in both treatment arms according to the requirements in the product information or the Pharmaceuticals Directive for off-label use (Annex VI to Section K). Carboplatin was used 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 for patients with non-squamous histology.

Treatment was given until disease progression, complete response, occurrence of unacceptable side effects or study discontinuation.

The primary endpoint of the study was overall survival. Patient-relevant secondary endpoints were AEs.

The pharmaceutical company uses the results of 2 sub-populations for the data cut-off of the 2nd interim analysis of 26.02.2018 for the adjusted indirect comparison.

The sub-populations of the KEYNOTE 042 study presented by the pharmaceutical company for the benefit assessment include, on the one hand, patients with non-squamous histology, PD-L1 expression ≥ 50% and a chemotherapy regimen consisting of carboplatin + pemetrexed. On the other, analyses are presented for patients with squamous histology, PD-L1 expression ≥

50% and a chemotherapy regimen consisting of carboplatin + paclitaxel. These analyses are based on the benefit assessment procedures 2019-04-01-D-447 and 2019-04-01-D-448.

On the indirect comparisons

For the proof of additional benefit, the pharmaceutical company submits evaluations depending on the histology of the NSCLC and accordingly differentiates between patients with squamous and non-squamous NSCLC.

For the corresponding adjusted indirect comparisons depending on histology, platinum-based chemotherapy was chosen by the pharmaceutical company as a bridge comparator. In the EMPOWER-Lung 3, KEYNOTE 024 and KEYNOTE 042 studies, different chemotherapy regimens were possible. In order to enable an indirect comparison, the pharmaceutical company therefore restricts these different chemotherapy regimens to individual therapy options:

For the statements on patients with non-squamous NSCLC, the pharmaceutical company uses the bridge comparators pemetrexed + carboplatin or cisplatin and considers the sub-populations of patients with PD-L1 expression ≥ 50% and non-squamous histology of the EMPOWER-Lung 3 study and the KEYNOTE 024 and KEYNOTE 042 studies. The results of the KEYNOTE studies on pembrolizumab monotherapy comparator therapy are meta-analytically summarised by the pharmaceutical company for the indirect comparison.

For the statements on patients with squamous NSCLC, the pharmaceutical company uses the bridge comparator paclitaxel + carboplatin and considers a sub-population of patients with PD-L1 expression ≥ 50% and squamous histology from the EMPOWER-Lung 3 study and the KEYNOTE 042 study.

For the formation of the corresponding sub-populations from both KEYNOTE studies, the pharmaceutical company again only used the results of those patients for the adjusted indirect comparison for whom carboplatin was a suitable therapy option according to a retrospective survey. In this survey, the principal investigator should justify the decision for treatment with carboplatin-based combination chemotherapy on a patient-individual basis. The comparator population is thus limited to patients who, in the opinion of the principal investigator, were unsuitable for cisplatin-based therapy and were therefore treated with carboplatin or would have been suitable for cisplatin-based therapy, but should be treated with carboplatin-based therapy due to the expected better benefit-risk ratio.

No such limitation of populations based on the use of carboplatin was made for the EMPOWER-Lung 3 study. In this regard, the pharmaceutical company pointed out in the written statement procedure that only 32 of 217 (14.7%) patients in the intervention arm of the EMPOWER-Lung 3- study were treated with a cisplatin-containing combination.

On the question of whether the criteria for or against therapy with carboplatin or cisplatin have changed in current clinical practice compared to the criteria used in the retrospective survey and consequently have an influence on the comparability of the sub-populations, it was pointed out in the statement by the clinical experts that there are no relevant changes in this regard and that this decision is dependent on contraindications and in particular also on the institution.

However, when assessing the suitability of the indirect comparisons, the G-BA also takes into account that the post-hoc limitations (based on the chemotherapy regimen and the retrospective survey on carboplatin) result in relevant percentages of the study populations of the KEYNOTE studies not being included in the analyses. Thus, in the KEYNOTE studies, this retrospective limitation of the study population meant that between 34% and 43% of patients

in the intervention and comparator arms who were assigned to therapy with carboplatin were not included in the analyses.

With regard to the similarity of the study populations as a central prerequisite for the consideration of studies in the adjusted indirect comparison, it can thus be stated that relevant uncertainties exist with regard to the comparability of the sub-populations of the KEYNOTE 024 and KEYNOTE 042 studies with the sub-population of the EMPOWER-Lung 3 study, as relevant percentages of the study populations of the KEYNOTE studies are not included in the analyses.

To address the uncertainties mentioned above, no further analyses based on the total populations of the KEYNOTE studies were submitted by the pharmaceutical company.

In the overall assessment, there are therefore relevant uncertainties regarding the comparability of the study populations, which is why the indirect comparisons submitted by the pharmaceutical company for patients with PD-L1 expression ≥ 50% are unsuitable for the benefit assessment.

Conclusion

For the assessment of the additional benefit of cemiplimab in combination with platinum-based chemotherapy versus pembrolizumab monotherapy in adults with locally advanced or metastatic NSCLC expressing PD L1 (in ≥ 50% of the tumour cells) with no EGFR, ALK or ROS1 aberrations, results from the adjusted indirect comparison of the EMPOWER-Lung 3 study with the KEYNOTE 024 and KEYNOTE 042 studies via the bridge comparator of platinum-based chemotherapy are available in the dossier.

For the formation of the corresponding sub-populations from the KEYNOTE studies, the pharmaceutical company only used the results of those patients for the adjusted indirect comparison for whom carboplatin was a suitable therapy option according to a retrospective survey. As a result, relevant percentages of the study populations of the KEYNOTE studies are not included in the analyses. No such limitation of populations based on the use of carboplatin was made for the EMPOWER-Lung 3 study. Thus, there are relevant uncertainties regarding the comparability of the study populations, so that the indirect comparisons are unsuitable for the benefit assessment.

In the overall assessment, an additional benefit of cemiplimab in combination with platinum-based chemotherapy compared to the appropriate comparator therapy for adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 50% of the tumour cells) with no genomic EGFR, ALK or ROS1 aberrations is not proven.

b) Adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 1% to < 50% of tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

An additional benefit is not proven.

Justification:

In the absence of direct comparator studies of cemiplimab in combination with platinum-based chemotherapy versus the appropriate comparator therapy, the pharmaceutical company uses two adjusted indirect comparisons according to the procedure of Bucher et al. for the proof of an additional benefit. For the adjusted indirect comparisons versus pembrolizumab in combination with platinum-based chemotherapy via the bridge comparator of platinum-based chemotherapy, the pharmaceutical company includes the

EMPOWER-Lung 3 study on the side of cemiplimab in combination with platinum-based chemotherapy and the KEYNOTE 189 and KEYNOTE 407 studies on the side of pembrolizumab in combination with platinum-based chemotherapy.

Description of the EMPOWER-Lung 3 study

For a detailed description of the EMPOWER-Lung 3 study, please refer to patient population a).

According to the marketing authorisation of cemiplimab + platinum-based chemotherapy, first-line treatment is limited to adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells).

For the benefit assessment, the pharmaceutical company therefore submitted evaluations on patients with PD-L1 expression of 1 to 49%. For the purpose of better comparability, the patient populations for the adjusted indirect comparison are additionally limited with regard to the chemotherapy regimen administered, resulting in 2 sub-populations for the analysis. In the case of non-squamous histology, only patients who were assigned to a chemotherapy combination of pemetrexed and carboplatin or cisplatin prior to randomisation were included in the analyses (53 vs 22 patients in the intervention and comparator arms). In the case of squamous histology, only patients who were assigned to a chemotherapy combination of paclitaxel and carboplatin prior to randomisation were considered (9 vs 23 patients in the intervention and comparator arms)

Description of the KEYNOTE 189 study

The KEYNOTE 189 study is an ongoing, double-blind, randomised, controlled phase III study comparing pembrolizumab + platinum-based chemotherapy with platinum-based chemotherapy, being conducted in 143 study sites, including in Europe and North America.

Adults with histologically or cytologically confirmed non-squamous metastatic NSCLC without EGFR mutation or ALK translocation were enrolled regardless of PD-L1 expression. Patients should be in good general condition (according to ECOG-PS ≤ 1) and must not have received prior systemic therapy for the metastatic stage.

Overall, stratified by platinum component (cisplatin/ carboplatin), PD-L1 expression (≥ 1%/ < 1%) and smoking status (never/ former and active), 616 patients were assigned in a 2:1 ratio to treatment with pembrolizumab + carboplatin or cisplatin and pemetrexed each (N = 410) or carboplatin or cisplatin only and pemetrexed (N = 206). The principal investigator selected the platinum-based chemotherapy prior to randomisation.

The administration of the study medication was carried out according to the requirements in the product information.

Patients are treated until disease progression, occurrence of unacceptable side effects or study discontinuation.

Primary endpoints of the study are PFS and overall survival. Patient-relevant secondary endpoints are endpoints on morbidity, health-related quality of life and AEs.

The pharmaceutical company uses the data cut-off of the 1st pre-specified interim analysis of 08.11.2017 for the adjusted indirect comparison.

According to the marketing authorisation of cemiplimab + platinum-based chemotherapy, first-line treatment is limited to adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells).

Therefore, evaluations of patients with PD-L1 expression of 1 to 49% are relevant for the benefit assessment.

For the benefit assessment, analyses of a sub-population of the KEYNOTE 189 study from the benefit assessment procedure 2019-04-01-D-447 are submitted by the pharmaceutical company.

Description of the KEYNOTE 407 study

The KEYNOTE 407 study is an ongoing, double-blind, randomised, controlled phase III study comparing pembrolizumab + carboplatin-based chemotherapy with carboplatin-based chemotherapy, being conducted in 125 study sites, including in Europe, North America and Asia.

Adults with histologically or cytologically confirmed squamous metastatic NSCLC were enrolled, regardless of PD-L1 expression. Patients should be in good general condition (according to ECOG-PS ≤ 1) and must not have received prior systemic therapy for the metastatic stage. For patients who had received adjuvant or neoadjuvant therapy, this had to have ended 12 months prior to formation of metastases.

Overall, stratified by type of taxane-based chemotherapy (paclitaxel/ nab-paclitaxel), PD-L1 expression (< 1%/ ≥ 1%) and geographic region (East Asia/ non-East Asia), 559 patients were assigned in a 1:1 ratio to treatment with pembrolizumab + carboplatin-based chemotherapy (N = 278) or carboplatin-based chemotherapy alone (N = 281).

Patients are treated until disease progression, complete response, occurrence of unacceptable side effects or study discontinuation.

Primary endpoints of the study are PFS and overall survival. Patient-relevant secondary endpoints are endpoints on morbidity, health-related quality of life and AEs.

The pharmaceutical company uses the data cut-off of the 2nd pre-specified interim analysis of 03.04.2018 for the adjusted indirect comparison.

According to the marketing authorisation of cemiplimab + platinum-based chemotherapy, first-line treatment is limited to adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells).

Therefore, evaluations of patients with PD-L1 expression of 1 to 49% are relevant for the benefit assessment.

For the benefit assessment, analyses of a sub-population of the KEYNOTE 407 study from the benefit assessment procedure 2019-04-01-D-448 are submitted by the pharmaceutical company.

On the indirect comparisons

For the proof of additional benefit, the pharmaceutical company submits evaluations depending on the histology of the NSCLC and accordingly differentiates between patients with squamous and non-squamous NSCLC.

For the corresponding adjusted indirect comparisons depending on histology, platinum-based chemotherapy was chosen by the pharmaceutical company as a bridge comparator:

For the adjusted indirect comparison of patients with non-squamous NSCLC, the pharmaceutical company chooses the bridge comparator pemetrexed + carboplatin or cisplatin and uses a sub-population from the EMPOWER-Lung 3 study and the KEYNOTE 189 study respectively.

For the adjusted indirect comparison of patients with squamous NSCLC, the pharmaceutical company chooses the bridge comparator paclitaxel + carboplatin and uses a sub-population from the EMPOWER-Lung 3 study and the KEYNOTE 407 study respectively.

For the formation of the corresponding sub-populations from both KEYNOTE studies, the pharmaceutical company only used the results of those patients for the adjusted indirect comparison for whom carboplatin was a suitable therapy option according to a retrospective survey. In this survey, the principal investigator should justify the decision for treatment with carboplatin-based combination chemotherapy on a patient-individual basis. The comparator population is thus limited to patients who, in the opinion of the principal investigator, were unsuitable for cisplatin-based therapy and were therefore treated with carboplatin or would have been suitable for cisplatin-based therapy, but should be treated with carboplatin-based therapy due to the expected better benefit-risk ratio.

No such limitation of populations based on the use of carboplatin was made for the EMPOWER-Lung 3 study. In this regard, the pharmaceutical company pointed out in the written statement procedure that only 32 of 217 (14.7%) patients in the intervention arm of the EMPOWER-Lung 3 study were treated with a cisplatin-containing combination.

On the question of whether the criteria for or against therapy with carboplatin or cisplatin have changed in current clinical practice compared to the criteria used in the retrospective survey and consequently have an influence on the comparability of the sub-populations, it was pointed out in the statement by the clinical experts that there are no relevant changes in this regard and that this decision is dependent on contraindications and in particular also on the institution.

However, when assessing the suitability of the indirect comparisons, the G-BA also takes into account that the post-hoc limitations (based on the chemotherapy regimen and the retrospective survey on carboplatin) result in relevant percentages of the study populations of the KEYNOTE studies not being included in the analyses. For example, in the KEYNOTE 407 study, this retrospective limitation of the study population meant that 23% of patients and in the KEYNOTE 189 study, 48% of patients in the intervention and comparator arms who were assigned therapy with carboplatin were not included in the analyses.

Based on the marketing authorisation of cemiplimab in combination with platinum-based chemotherapy, patient population b) also addresses patients with a PD-L1 expression of ≥ 1% to < 50%. However, the percentages of patients with PD-L1 expression < 1%, which - based on the marketing authorisation of cemiplimab in combination with platinum-based chemotherapy - are not subject to assessment, amount to 49% vs 52% in the KEYNOTE 189 study and 45% vs 50% in the intervention vs comparator arm in the KEYNOTE 407 study.

With regard to the similarity of the study populations as a central prerequisite for the consideration of studies in the adjusted indirect comparison, it can thus be stated that relevant uncertainties exist with regard to the comparability of the submitted sub-populations of the KEYNOTE 189 and KEYNOTE 407 studies with the sub-population of the EMPOWER-Lung 3 study, especially as relevant percentages of the study populations of the KEYNOTE studies are not included in the analyses.

To address the uncertainties mentioned above, no further analyses based on the total populations of the KEYNOTE studies were submitted by the pharmaceutical company.

In the overall assessment, there are therefore relevant uncertainties regarding the comparability of the study populations, which is why the indirect comparisons submitted by the pharmaceutical company for patients with PD-L1 expression ≥ 1% to < 50% are unsuitable for the benefit assessment.

Conclusion

For the assessment of the additional benefit of cemiplimab in combination with platinum-based chemotherapy versus pembrolizumab in combination with platinum-based chemotherapy in adults with locally advanced or metastatic NSCLC expressing PD L1 (in ≥ 1% to < 50% of tumour cells) with no EGFR, ALK or ROS1 aberrations, results from the adjusted indirect comparison of the EMPOWER-Lung 3 study with the KEYNOTE 189 and KEYNOTE 407 studies via the bridge-comparator of platinum-based chemotherapy are available in the dossier.

For the formation of the corresponding sub-populations from the KEYNOTE studies, the pharmaceutical company only used the results of those patients for the adjusted indirect comparison for whom carboplatin was a suitable therapy option according to a retrospective survey. As a result, relevant percentages of the study populations of the KEYNOTE studies are not included in the analyses. No such limitation of populations based on the use of carboplatin was made for the EMPOWER-Lung 3 study. Thus, there are relevant uncertainties regarding the comparability of the study populations, so that the indirect comparisons are unsuitable for the benefit assessment.

In addition, the evaluations presented include a relevant number of patients with PD-L1 expression < 1%, who - based on the marketing authorisation of cemiplimab in combination with platinum-based chemotherapy - are not subject to assessment.

In the overall assessment, an additional benefit of cemiplimab in combination with platinum-based chemotherapy compared to the appropriate comparator therapy for adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 1% to < 50% of the tumour cells) with no genomic EGFR, ALK or ROS1 aberrations is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Libtayo with the active ingredient cemiplimab.

The therapeutic indication assessed here is as follows:

"LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

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

In the therapeutic indication under consideration, 2 patient groups were distinguished and the appropriate comparator therapy was determined as follows (abbreviated version):

a) Adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 50% of tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

   The appropriate comparator therapy includes various immune checkpoint inhibitors, both as monotherapy and in combination with platinum-based chemotherapy.

b) Adults with locally advanced or metastatic NSCLC expressing PD-L1- (in ≥ 1% to < 50% of tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

The appropriate comparator therapy includes various platinum-based chemotherapies, partly in combination with an immune checkpoint inhibitor, as well as an immune checkpoint inhibitor as monotherapy.

Patient group a)

The pharmaceutical company submits an adjusted indirect comparison of cemiplimab in combination with platinum-based chemotherapy (EMPOWER-Lung 3 study) versus pembrolizumab (KEYNOTE 024 and KEYNOTE 042 studies) via the bridge comparator of platinum-based chemotherapy for assessment.

From the KEYNOTE studies, only the results of patients for whom carboplatin was a suitable therapy option according to a retrospective survey were used by the pharmaceutical company for the adjusted indirect comparison. Relevant percentages of the study populations of the KEYNOTE studies were therefore not included in the analyses. Such a limitation of the populations was not made for the EMPOWER-Lung 3 study. There are thus relevant uncertainties between the studies presented with regard to the comparability of the study populations, so that the indirect comparisons are unsuitable for the benefit assessment.

In the overall assessment, an additional benefit of cemiplimab in combination with platinum-based chemotherapy compared to the appropriate comparator therapy for adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 50% of the tumour cells) with no EGFR-, ALK or ROS1 aberrations is not proven.

Patient group b)

The pharmaceutical company submits an adjusted indirect comparison of cemiplimab in combination with platinum-based chemotherapy (EMPOWER-Lung 3 study) versus pembrolizumab in combination with platinum-based chemotherapy (KEYNOTE 189 and KEYNOTE 407 studies) via the bridge comparator of platinum-based chemotherapy for assessment.

From the KEYNOTE studies, only the results of patients for whom carboplatin was a suitable therapy option according to a retrospective survey were used by the pharmaceutical company for the adjusted indirect comparison. Relevant percentages of the study populations of the KEYNOTE studies were therefore not included in the analyses. Such a limitation of the populations was not made for the EMPOWER-Lung 3 study.

In addition, the evaluations presented include a relevant number of patients with PD-L1 expression < 1%, who - based on the marketing authorisation of cemiplimab in combination with platinum-based chemotherapy - are not subject to assessment.

There are therefore relevant uncertainties between the studies presented with regard to the comparability of the study populations, so that the indirect comparisons are unsuitable for the benefit assessment.

In the overall assessment, an additional benefit of cemiplimab in combination with platinum-based chemotherapy compared to the appropriate comparator therapy for adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 1% to < 50% of the tumour cells) with no genomic EGFR, ALK or ROS1 aberrations 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).

For the number of German patients with lung cancer, the projected incidence for 2022 (59,700 patients)[2] is used as the basis for the calculations.

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 between 73.6% and 83.6%[3] (4,939 to 49,909 patients).
2. Of these, 46.63% of patients are in stage IV at initial diagnosis[4]. Of the remaining 53.37% of patients who are in stage I-IIIB, 37.7% will progress to stage IV in 2022[5]. The percentage of patients in stage IIIB/IIIC is 4.5% to 6.1%[6]. The total number of patients is 32,017 to 36,985.
3. First-line therapy is given in 76.9% to 96.1%[3] of cases (24,076 - 34,964 patients).
4. The percentage of patients with no EGFR mutation is 85.8% - 89.7%[7,8]. The percentage of patients with no ALK translocation is 94.9% - 98.0%[8]. The percentage of patients with BRAF V600 mutation is 0.6% - 1.2%[9]. The percentage of patients with RET fusion is 0.6% - 0.9%[10]. The percentage of patients with no ROS translocation is 96.3% - 98.5%[8]. Overall, the percentage of patients with no EGFR mutation, with no ALK translocation, with no BRAF V600 mutation, with no RET fusion and with no ROS translocation is 74.9% - 85.0% (20,464 to 26,188 patients).
5. The percentage of patients with PD-L1 expression ≥ 50% of tumour cells is 25.9% to 28.9%[8] (5,300 to 7,568 patients) and PD-L1 expression ≥ 1% to < 50% of tumour cells is 26.9%[6] (5,505 to 7,045 patients).
6. Considering 88.3% of patients are insured by the SHI, there are 18,070 to 23,124 patients in the first-line therapy (PD-L1 expression ≥ 50%: 4,680 to 6,683 patients; PD-L1 expression ≥ 1% to < 50%: 4,861 to 6,220 patients).

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

2 Robert Koch Institute, Society of Epidemiological Cancer Registries in Germany. Cancer in Germany for 2017/2018. 2021

3 Benefit assessment according to Section 35a SGB V, A21-27, selpercatinib, 11.06.2021

4 Benefit assessment according to Section 35a SGB V, A23-29 | A23-31, durvalumab and tremelimumab, 29.06.2023

5 Tumour Registry Munich ICD-10 C34: Non-small cell. BC Survival [online]. 2022. URL: https://www.tumorregister-muenchen.de/facts/surv/sC34N_G-ICD-10-C34-Nicht-kleinzell.-BC-Survival.pdf; 37.7% (for the longest possible observation period of 15 years)

6 Benefit assessment according to Section 35a SGB V, A23-37, cemiplimab, 28.04.2023

7 Benefit assessment according to Section 35a SGB V, A21-86, osimertinib, 29.09.2021

8 Benefit assessment according to Section 35a SGB V, A21-98, cemiplimab, 28.10.2021

9 2nd addendum to the benefit assessment according to Section 35a SGB V, A23-29 | A23-31, durvalumab and tremelimumab, 31.08.2023

10 Benefit assessment according to Section 35a SGB V, A21-27, selpercatinib, 11.06.2021

product characteristics, SmPC) for Libtayo (active ingredient: cemiplimab) at the following publicly accessible link (last access: 20 July 2023):

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

Treatment with cemiplimab 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 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.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card).

The training material contains, in particular, information and warnings about immune-mediated side effects as well as infusion-related reactions.

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

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: 1 October 2023).

When atezolizumab is administered in combination with bevacizumab, paclitaxel and carboplatin, atezolizumab is administered 840 mg every two weeks or 1,200 mg every three weeks or 1,680 mg every four weeks in the induction and maintenance phase – initially in a four or six-cycle induction phase in combination with bevacizumab, paclitaxel and carboplatin every three weeks, followed by a maintenance phase in combination with bevacizumab every three weeks.

When atezolizumab is administered in combination with nab-paclitaxel and carboplatin, atezolizumab is given 840 mg every two weeks or 1,200 mg every three weeks or 1,680 mg every four weeks in the induction and maintenance phase, given in a four or six-cycle induction phase in combination with carboplatin every three weeks and nab-paclitaxel every three weeks on day 1, 8 and 15, followed by the maintenance phase with atezolizumab monotherapy.

For the use of carboplatin as combination therapy in advanced NSCLC, Annex VI to Section K of the Pharmaceuticals Directive specifies a dosage of up to 500 mg/m^2 BSA or AUC 6.0 mg/ml x min (Area Under the Curve). In combination with nab-paclitaxel, the product information also refers to a dosage of AUC 6.0 mg/ml x min.

Cisplatin is dosed differently, depending on the concomitant active ingredient. According to the product information of the concomitant active ingredient, the single dose of cisplatin in combination with pemetrexed is 75 mg/m² BSA and in combination with paclitaxel 80 mg/m² BSA.

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.

For nivolumab, the recommended dose is 360 mg every 3 weeks in combination with 1 mg/kg BW ipilimumab every 6 weeks and platinum-based chemotherapy every 3 weeks, whereby treatment with 360 mg nivolumab intravenously every 3 weeks in combination with 1 mg/kg ipilimumab intravenously every 6 weeks continues after 2 cycles of chemotherapy.

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 varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number 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:

a) Adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

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 + platinum-based chemotherapy[11]				
Cemiplimab	1 x per 21-day cycle	17.4	1	17.4
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Monotherapies				
Atezolizumab	1 x per 14-day cycle	26.1	1	26.1
	or			
	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 28-day cycle	13.0	1	13.0
Cemiplimab	1 x per 21-day cycle	17.4	1	17.4

11 The treatment options for platinum-based chemotherapy were carboplatin or cisplatin in combination with paclitaxel or pemetrexed.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)				
Nivolumab	1 x per 21-day cycle	17.4	1	17.4
Ipilimumab	1 x per 42-day cycle	8.7	1	8.7
Cisplatin	1 x per 21-day cycle	2	1	2.0
Carboplatin	1 x per 21-day cycle	2	1	2.0
Pemetrexed	1 x per 21-day cycle	2	1	2.0
Paclitaxel	1 x per 21-day cycle	2	1	2.0
Atezolizumab + bevacizumab + paclitaxel + carboplatin (only for patients with ECOG PS 0-1 and non-squamous NSCLC)				
Induction therapy				
Atezolizumab	1 x per 14-day cycle	4 - 6	1	4.0 - 6.0
	or			
	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
	or			
	1 x per 28-day cycle	4 - 6	1	4.0 - 6.0
Bevacizumab	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
Paclitaxel	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
Carboplatin	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
Maintenance treatment[12]				
Atezolizumab	1 x per 14-day cycle	20.1 - 22.1	1	20.1 - 22.1
	or			
	1 x per 21-day cycle	11.4 - 13.4	1	11.4 - 13.4
	or			
	1 x per 28-day cycle	7 - 9	1	7.0 - 9.0

12 The number and ranges of the cycles of the respective maintenance treatments result from the total number and ranges of the respective therapy cycles of a whole treatment year minus the number and ranges of the cycles of the respective induction therapy.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Bevacizumab	1 x per 21-day cycle	11.4 - 13.4	1	11.4 - 13.4
Atezolizumab + carboplatin + nab-paclitaxel *(only for patients with ECOG PS 0-1 and non-squamous NSCLC)*				
Induction				
Atezolizumab	1 x per 14-day cycle	4 - 6	1	4.0 - 6.0
	or			
	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
	or			
	1 x per 28-day cycle	4 - 6	1	4.0 - 6.0
Carboplatin	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
nab-paclitaxel	3 x per 21-day cycle	4 - 6	3	12.0 - 18.0
Maintenance treatment[12]				
Atezolizumab	1 x per 14-day cycle	20.1 - 22.1	1	20.1 - 22.1
	or			
	1 x per 21-day cycle	11.4 - 13.4	1	11.4 - 13.4
	or			
	1 x per 28-day cycle	7 - 9	1	7.0 - 9.0
Pembrolizumab + carboplatin + (nab)-paclitaxel *(only for patients with ECOG-PS 0-1 and squamous NSCLC)*				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
nab-paclitaxel	3 x per 21-day cycle	17.4	3	52.2
Pembrolizumab + pemetrexed + platinum-containing chemotherapy *(only for patients with ECOG-PS 0-1 and non-squamous NSCLC)*				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Carboplatin	1 x per 21-day cycle	17.4	1	17.4

b) Adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 1% to < 50% of tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

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 + platinum-based chemotherapy[11]				
Cemiplimab	1 x per 21-day cycle	17.4	1	17.4
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Atezolizumab monotherapy				
Atezolizumab	1 x per 14-day cycle	26.1	1	26.1
	or			
	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 28-day cycle	13.0	1	13.0
Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)				
Nivolumab	1 x per 21-day cycle	17.4	1	17.4
Ipilimumab	1 x per 42-day cycle	8.7	1	8.7
Cisplatin	1 x per 21-day cycle	2	1	2.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Carboplatin	1 x per 21-day cycle	2	1	2.0
Pemetrexed	1 x per 21-day cycle	2	1	2.0
Paclitaxel	1 x per 21-day cycle	2	1	2.0
Atezolizumab + bevacizumab + paclitaxel + carboplatin (only for patients with ECOG PS 0-1 and non-squamous NSCLC)				
Induction therapy				
Atezolizumab	1 x per 14-day cycle	4 - 6	1	4.0 - 6.0
	or			
	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
	or			
	1 x per 28-day cycle	4 - 6	1	4.0 - 6.0
Bevacizumab	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
Paclitaxel	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
Carboplatin	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
Maintenance treatment[12]				
Atezolizumab	1 x per 14-day cycle	20.1 - 22.1	1	20.1 - 22.1
	or			
	1 x per 21-day cycle	11.4 - 13.4	1	11.4 - 13.4
	or			
	1 x per 28-day cycle	7 - 9	1	7.0 - 9.0
Bevacizumab	1 x per 21-day cycle	11.4 - 13.4	1	11.4 - 13.4
Atezolizumab + carboplatin + nab-paclitaxel (only for patients with ECOG PS 0-1 and non-squamous NSCLC)				
Induction				
Atezolizumab	1 x per 14-day cycle	4 - 6	1	4.0 - 6.0
	or			
	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0
	or			
	1 x per 28-day cycle	4 - 6	1	4.0 - 6.0
Carboplatin	1 x per 21-day cycle	4 - 6	1	4.0 - 6.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
nab-paclitaxel	3 x per 21-day cycle	4 - 6	3	12.0 - 18.0
Maintenance treatment[12]				
Atezolizumab	1 x per 14-day cycle	20.1 - 22.1	1	20.1 - 22.1
	or			
	1 x per 21-day cycle	11.4 - 13.4	1	11.4 - 13.4
	or			
	1 x per 28-day cycle	7 - 9	1	7.0 - 9.0
Pembrolizumab + carboplatin + (nab)-paclitaxel (only for patients with ECOG-PS 0-1 and squamous NSCLC)				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
nab-paclitaxel	3 x per 21-day cycle	17.4	3	52.2
Pembrolizumab + pemetrexed + platinum-containing chemotherapy (only for patients with ECOG-PS 0-1 and non-squamous NSCLC)				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Carboplatin + nab-paclitaxel (only for patients with ECOG-PS 2)				
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
nab-paclitaxel	3 x per 21-day cycle	17.4	3	52.2
Carboplatin + third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) cf. Annex VI to Section K of the Pharmaceuticals Directive				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
(only for patients with ECOG-PS 2)				
Carboplatin	1 x per 21-day cycle	17.4	1	17.4
Gemcitabine	2 x per 21-day cycle	17.4	2	34.8
Vinorelbine	2 x per 21-day cycle	17.4	2	34.8
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4

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.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).[13]

a) Adults with locally advanced or metastatic NSCLC expressing PD-L1- (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

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 + platinum-based chemotherapy[11]					
Cemiplimab	350 mg	350 mg	1 x 350 mg	17.4	17.4 x 350 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 1 x 450 mg	17.4	17.4 x 600 mg + 17.4 x 450 mg
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 50 mg + 1 x 100 mg	17.4	17.4 x 50 mg + 17.4 x 100 mg
	80 mg/m²	152 mg	1 x 10 mg +	17.4	17.4 x 10 mg +

13 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	= 152 mg		1 x 50 mg + 1 x 100 mg		17.4 x 50 mg + 17.4 x 100 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 mg + 1 x 150 mg	17.4	34.8 x 100 mg + 17.4 x 150 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Appropriate comparator therapy					
Monotherapies					
Atezolizumab	840 mg	840 mg	1 x 840 mg	26.1	26.1 x 840 mg
	or				
	1,200 mg	1,200 mg	1 x 1,200 mg	17.4	17.4 x 1,200 mg
	or				
	1,680 mg	1,680 mg	2 x 840 mg	13.0	26 x 840 mg
Cemiplimab	350 mg	350 mg	1 x 350 mg	17.4	17.4 x 350 mg
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
Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)					
Nivolumab	360 mg	360 mg	3 x 120 mg	17.4	52.2 x 120 mg
Ipilimumab	1 mg/kg = 77 mg	77 mg	2 x 50 mg	8.7	17.4 x 50 mg
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 50 mg + 1 x 100 mg	2.0	2 x 50 mg + 2 x 100 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 450 mg + 1 x 600 mg	2.0	2 x 450 mg + 2 x 600 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	2.0	4 x 500 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 mg + 1 x 150 mg	2.0	4.0 x 100 mg + 2.0 x 150 mg
Atezolizumab + bevacizumab + paclitaxel + carboplatin					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
(only for patients with ECOG PS 0-1 and non-squamous NSCLC)					
Induction therapy					
Atezolizumab	840 mg	840 mg	1 x 840 mg	4.0 – 6.0	4.0 x 840 mg or 6.0 x 840 mg
	or				
	1,200 mg	1,200 mg	1 x 1,200 mg	4.0 – 6.0	4.0 x 1,200 mg or 6.0 x 1,200 mg
	or				
	1,680 mg	1,680 mg	2 x 840 mg	4.0 – 6.0	8.0 x 840 mg or 12.0 x 840 mg
Bevacizumab	7.5 mg/kg = 577.5 mg	577.5 mg	1 x 400 mg + 2 x 100 mg – 1 x 400 mg + 2 x 100 mg	4.0 - 6.0	4.0 x 400 mg + 8.0 x 100 mg – 6.0 x 400 mg + 12.0 x 100 mg
	or				
	15 mg/kg = 1,155 mg	1,155 mg	3 x 400 mg	4.0 - 6.0	12.0 x 400 mg – 18.0 x 400 mg
Paclitaxel	175 mg/m^2 = 332.5 mg	332.5 mg	1 x 150 mg + 2 x 100 mg – 1 x 150 mg + 2 x 100 mg	4.0 - 6.0	4.0 x 150 mg + 8.0 x 100 mg – 6.0 x 150 mg + 12.0 x 100 mg
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 x 600 mg + 1 x 450 mg – 1 x 600 mg + 1 x 450 mg	4.0 - 6.0	4.0 x 600 mg + 4.0 x 450 mg – 6.0 x 600 mg + 6.0 x 450 mg
Maintenance treatment[12]					
Atezolizumab	840 mg	840 mg	1 x 840 mg	20.1 – 22.1	22.1 x 840 mg – 20.1 x 840 mg
	or				
	1,200 mg	1,200 mg	1 x 1,200 mg	11.4 – 13.4	13.4 x 1,200 mg – 11.4 x 1,200 mg
	or				

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	1,680 mg	1,680 mg	2 x 840 mg	7 - 9	18.0 x 840 mg – 14.0 x 840 mg
Bevacizumab	7.5 mg/kg = 577.5 mg	577.5 mg	1 x 400 mg + 2 x 100 mg	11.4 – 13.4	11.4 x 400 mg + 22.8 x 100 mg – 13.4 x 400 mg + 26.8 x 100 mg
	or				
	15 mg/kg = 1,155 mg	1,155 mg	3 x 400 mg	11.4 – 13.4	34.2 x 400 mg – 40.2 x 400 mg
Atezolizumab + carboplatin + nab-paclitaxel *(only for patients with ECOG PS 0-1 and non-squamous NSCLC)*					
Induction					
Atezolizumab	840 mg	840 mg	1 x 840 mg	4.0 – 6.0	4.0 x 840 mg – 6.0 x 840 mg
	or				
	1,200 mg	1,200 mg	1 x 1,200 mg	4.0 – 6.0	4.0 x 1,200 mg – 6.0 x 1,200 mg
	or				
	1,680 mg	1,680 mg	2 x 840 mg	4.0 – 6.0	8.0 x 840 mg – 12.0 x 840 mg
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 x 600 mg + 1 x 450 mg	4.0 – 6.0	4.0 x 600 mg + 4.0 x 450 mg – 6.0 x 600 mg + 6.0 x 450 mg
nab-paclitaxel	100 mg/m^2 = 190 mg	190 mg	2 x 100 mg	12 – 18	24 x 100 mg – 36 x 100 mg
Maintenance[12]					
Atezolizumab	840 mg	840 mg	1 x 840 mg	20.1 – 22.1	22.1 x 840 mg – 20.1 x 840 mg
	or				
	1,200 mg	1,200 mg	1 x 1,200 mg	11.4 –	13.4 x 1,200 mg –

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
				13.4	11.4 x 1,200 mg
	or				
	1,680 mg	1,680 mg	2 x 840 mg	7 – 9	18.0 x 840 mg – 14.0 x 840 mg
Pembrolizumab + carboplatin + (nab)-paclitaxel *(only for patients with ECOG-PS 0-1 and squamous NSCLC)*					
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
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 x 450 mg + 1 x 600 mg	17.4	17.4 x 450 mg + 17.4 x 600 mg
Paclitaxel	175 mg/m^2 = 332.5 mg	332.5 mg	2 x 100 mg + 1 x 150 mg	17.4	34.8 x 100 mg + 17.4 x 150 mg
nab-paclitaxel	100 mg/m^2 = 190 mg	190 mg	2 x 100 mg	52.2	104.4 x 100 mg
Pembrolizumab + pemetrexed + platinum-containing chemotherapy *(only for patients with ECOG-PS 0-1 and non-squamous NSCLC)*					
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
Pemetrexed	500 mg/m^2 = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 x 450 mg + 1 x 600 mg	17.4	17.4 x 450 mg + 17.4 x 600 mg
Cisplatin	75 mg/m^2 = 142.5 mg	142.5 mg	1 x 50 mg + 1 x 100 mg	17.4	17.4 x 50 mg + 17.4 x 100 mg

b) <u>Adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 1% to < 50% of tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy</u>

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 + platinum-based chemotherapy[11]					
Cemiplimab	350 mg	350 mg	1 x 350 mg	17.4	17.4 x 350 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 1 x 450 mg	17.4	17.4 x 600 mg + 17.4 x 450 mg
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 50 mg + 1 x 100 mg	17.4	17.4 x 50 mg + 17.4 x 100 mg
	80 mg/m² = 152 mg	152 mg	1 x 10 mg + 1 x 50 mg + 1 x 100 mg	17.4	17.4 x 10 mg + 17.4 x 50 mg + 17.4 x 100 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 mg + 1 x 150 mg	17.4	34.8 x 100 mg + 17.4 x 150 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Appropriate comparator therapy					
Monotherapy					
Atezolizumab	840 mg	840 mg	1 x 840 mg	26.1	26.1 x 840 mg
	or				
	1,200 mg	1,200 mg	1 x 1,200 mg	17.4	17.4 x 1,200 mg
	or				
	1,680 mg	1,680 mg	2 x 840 mg	13.0	26 x 840 mg
Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1)					
Nivolumab	360 mg	360 mg	3 x 120 mg	17.4	52.2 x 120 mg
Ipilimumab	1 mg/kg = 77 mg	77 mg	2 x 50 mg	8.7	17.4 x 50 mg
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 50 mg + 1 x 100 mg	2.0	2 x 50 mg + 2 x 100 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 450 mg + 1 x 600 mg	2.0	2 x 450 mg + 2 x 600 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	2.0	4 x 500 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 mg + 1 x 150 mg	2.0	4.0 x 100 mg + 2.0 x 150 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Atezolizumab + bevacizumab + paclitaxel + carboplatin (only for patients with ECOG PS 0-1 and non-squamous NSCLC)					
Induction therapy					
Atezolizumab	840 mg	840 mg	1 x 840 mg	4.0 – 6.0	4.0 x 840 mg – 6.0 x 840 mg
	or				
	1,200 mg	1,200 mg	1 x 1,200 mg	4.0 – 6.0	4.0 x 1,200 mg – 6.0 x 1,200 mg
	or				
	1,680 mg	1,680 mg	2 x 840 mg	4.0 – 6.0	8.0 x 840 mg – 12.0 x 840 mg
Bevacizumab	7.5 mg/kg = 577.5 mg	577.5 mg	1 x 400 mg + 2 x 100 mg	4.0 – 6.0	4.0 x 400 mg + 8.0 x 100 mg – 6.0 x 400 mg + 12.0 x 100 mg
	or				
	15 mg/kg = 1,155 mg	1,155 mg	3 x 400 mg	4.0 – 6.0	12.0 x 400 mg – 18.0 x 400 mg
Paclitaxel	175 mg/m^2 = 332.5 mg	332.5 mg	1 x 150 mg + 2 x 100 mg	4.0 – 6.0	4.0 x 150 mg + 8.0 x 100 mg – 6.0 x 150 mg + 12.0 x 100 mg
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 x 600 mg + 1 x 450 mg	4.0 – 6.0	4.0 x 600 mg + 4.0 x 450 mg – 6.0 x 600 mg + 6.0 x 450 mg
Maintenance treatment[12]					
Atezolizumab	840 mg	840 mg	1 x 840 mg	22.1 – 20.1	22.1 x 840 mg – 20.1 x 840 mg
	or				
	1,200 mg	1,200 mg	1 x 1,200 mg	13.4 – 11.4	13.4 x 1,200 mg – 11.4 x 1,200 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	or				
	1,680 mg	1,680 mg	2 x 840 mg	9 – 7	18.0 x 840 mg – 14.0 x 840 mg
Bevacizumab	7.5 mg/kg = 577.5 mg	577.5 mg	1 x 400 mg + 2 x 100 mg	11.4 – 13.4	11.4 x 400 mg + 22.8 x 100 mg – 13.4 x 400 mg + 26.8 x 100 mg
	or				
	15 mg/kg = 1,155 mg	1,155 mg	3 x 400 mg	11.4 – 13.4	34.2 x 400 mg – 40.2 x 400 mg
Atezolizumab + carboplatin + nab-paclitaxel *(only for patients with ECOG PS 0-1 and non-squamous NSCLC)*					
Induction					
Atezolizumab	840 mg	840 mg	1 x 840 mg	4.0 – 6.0	4.0 x 840 mg – 6.0 x 840 mg
	or				
	1,200 mg	1,200 mg	1 x 1,200 mg	4.0 – 6.0	4.0 x 1,200 mg – 6.0 x 1,200 mg
	or				
	1,680 mg	1,680 mg	2 x 840 mg	4.0 – 6.0	8.0 x 840 mg – 12.0 x 840 mg
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 x 600 mg + 1 x 450 mg	4.0 – 6.0	4.0 x 600 mg + 4 x 450 mg – 6 x 600 mg + 6 x 450 mg
nab-paclitaxel	100 mg/m^2 = 190 mg	190 mg	2 x 100 mg	12 – 18	24 x 100 mg – 36 x 100 mg
Maintenance[12]					
Atezolizumab	840 mg	840 mg	1 x 840 mg	22.1 – 20.1	22.1 x 840 mg – 20.1 x 840 mg
	or				

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	1,200 mg	1,200 mg	1 x 1,200 mg	13.4 – 11.4	13.4 x 1,200 mg – 11.4 x 1,200 mg
	or				
	1,680 mg	1,680 mg	2 x 840 mg	9 – 7	18.0 x 840 mg – 14.0 x 840 mg
Pembrolizumab + carboplatin + (nab)-paclitaxel (only for patients with ECOG-PS 0-1 and squamous NSCLC)					
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
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 x 450 mg + 1 x 600 mg	17.4	17.4 x 450 mg + 17.4 x 600 mg
Paclitaxel	175 mg/m^2 = 332.5 mg	332.5 mg	2 x 100 mg + 1 x 150 mg	17.4	34.8 x 100 mg + 17.4 x 150 mg
nab-paclitaxel	100 mg/m^2 = 190 mg	190 mg	2 x 100 mg	52.2	104.4 x 100 mg
Pembrolizumab + pemetrexed + platinum-containing chemotherapy (only for patients with ECOG-PS 0-1 and non-squamous NSCLC)					
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
Pemetrexed	500 mg/m^2 = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 x 450 mg + 1 x 600 mg	17.4	17.4 x 450 mg + 17.4 x 600 mg
Cisplatin	75 mg/m^2 = 142.5 mg	142.5 mg	1 x 50 mg + 1 x 100 mg	17.4	17.4 x 50 mg + 17.4 x 100 mg
Carboplatin + nab-paclitaxel (only for patients with ECOG-PS 2)					
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 x 450 mg + 1 x 600 mg	17.4	17.4 x 450 mg + 17.4 x 600 mg
nab-paclitaxel	100 mg/m^2 = 190 mg	190 mg	2 x 100 mg	52.2	104.4 x 100 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Carboplatin + third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) cf. Annex VI to Section K of the Pharmaceuticals Directive (only for patients with ECOG-PS 2)					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 450 mg + 1 x 600 mg	17.4	17.4 x 450 mg + 17.4 x 600 mg
Gemcitabine	1,250 mg/m² = 2,375 mg	2,375 mg	2 x 200 mg + 2 x 1,000 mg	34.8	69.6 x 200 mg + 69.6 x 1,000 mg
Vinorelbine	25 mg/m² – 30 mg/m² = 47.5 mg – 57 mg	47.5 mg – 57 mg	1 x 50 mg – 1 x 50 mg + 1 x 10 mg	34.8	34.8 x 50 mg – 34.8 x 50 mg + 34.8 x 10 mg
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 mg + 1 x 150 mg	17.4	34.8 x 100 mg + 17.4 x 150 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg

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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

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 350 mg	1 CIS	€ 5,148.68	€ 2.00	€ 498.43	€ 4,648.25
Carboplatin 600 mg	1 CIS	€ 300.84	€ 2.00	€ 13.74	€ 285.10
Carboplatin 450 mg	1 CIS	€ 228.24	€ 2.00	€ 10.29	€ 215.95
Cisplatin 10 mg	1 CIS	€ 18.60	€ 2.00	€ 0.35	€ 16.25
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12

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
Cisplatin 100 mg	1 CIS	€ 84.13	€ 2.00	€ 9.22	€ 72.91
Pemetrexed 500 mg	1 PCI	€ 517.04	€ 2.00	€ 24.00	€ 491.04
Paclitaxel 150 mg	1 CIS	€ 428.97	€ 2.00	€ 19.82	€ 407.15
Paclitaxel 100 mg	1 CIS	€ 289.47	€ 2.00	€ 13.20	€ 274.27
Appropriate comparator therapy					
Atezolizumab 840 mg	1 CIS	€ 2,907.75	€ 2.00	€ 279.03	€ 2,626.72
Atezolizumab 1,200 mg	1 CIS	€ 4,129.23	€ 2.00	€ 398.62	€ 3,728.61
Bevacizumab 400 mg	1 CIS	€ 1,553.33	€ 2.00	€ 146.43	€ 1,404.90
Bevacizumab 100 mg	1 CIS	€ 397.02	€ 2.00	€ 36.61	€ 358.41
Carboplatin 600 mg	1 CIS	€ 300.84	€ 2.00	€ 13.74	€ 285.10
Carboplatin 450 mg	1 CIS	€ 228.24	€ 2.00	€ 10.29	€ 215.95
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12
Cisplatin 100 mg	1 CIS	€ 84.13	€ 2.00	€ 9.22	€ 72.91
Cemiplimab 350 mg	1 CIS	€ 5,148.68	€ 2.00	€ 498.43	€ 4,648.25
Docetaxel 160 mg	1 CIS	€ 515.78	€ 2.00	€ 23.94	€ 489.84
Gemcitabine 200 mg	1 PIF	€ 28.85	€ 2.00	€ 0.83	€ 26.02
Gemcitabine 1000 mg	1 PIF	€ 102.35	€ 2.00	€ 10.62	€ 89.73
Ipilimumab 50 mg	1 CIS	€ 3,489.23	€ 2.00	€ 335.96	€ 3,151.27
Paclitaxel 150 mg	1 CIS	€ 428.97	€ 2.00	€ 19.82	€ 407.15
Paclitaxel 100 mg	1 CIS	€ 289.47	€ 2.00	€ 13.20	€ 274.27
nab-paclitaxel 100 mg	1 PIS	€ 429.36	€ 2.00	€ 19.84	€ 407.52
Nivolumab 120 mg	1 CIS	€ 1,546.96	€ 2.00	€ 145.81	€ 1,399.15
Pembrolizumab 100 mg	1 CIS	€ 2,974.82	€ 2.00	€ 285.60	€ 2,687.22
Pemetrexed 500 mg	1 PCI	€ 517.04	€ 2.00	€ 24.00	€ 491.04
Vinorelbine 50 mg	10 CIS	€ 1,424.56	€ 2.00	€ 67.07	€ 1,355.49
Vinorelbine 10 mg	10 CIS	€ 294.01	€ 2.00	€ 13.42	€ 278.59
Abbreviations: CIS = concentrate for the preparation of an infusion solution; PCI = powder for a concentrate for the preparation of an infusion solution, PIF = powder for the preparation of an infusion solution; PIS = powder for the preparation of an infusion suspension					

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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.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

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	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed							
Cisplatin							
17.4 cycles of 21 days each (Cemiplimab + platinum-based chemotherapy)							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Hydration and forced diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
Sodium chloride 0.9% Inf. Solution, 3 l - 4.4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	17.4	€ 170.07 - € 263.11
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Pemetrexed							
17.4 cycles of 21 days each (Cemiplimab + platinum-based chemotherapy)							
Dexamethasone [14] 2 x 4 mg	100 x 4 mg TAB	€ 79.54	€ 2.00	€ 5.40	€ 72.14	52.2	€ 75.31

14 Fixed reimbursement rate

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	Treatment days/ year	Costs/ patient/ year
Folic acid [15] 350 – 1,000 µg/day	30 x 400 µg SFI	€ 3.10	€ 0.00	€ 0.00	€ 3.10	365.0	€ 37.72 - € 75.43
Vitamin B12 [14] 1,000 µg/day, every 3 cycles	10 x 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.32	€ 6.71	5.8	€ 3.89
Paclitaxel							
17.4 cycles of 21 days each (Cemiplimab + platinum-based chemotherapy)							
Dexamethasone [14] 2 x 20 mg	50 x 20 mg TAB	€ 118.88	€ 2.00	€ 0.00	€ 116.88	17.4	€ 81.35
Dimetindene IV 1 mg/10 kg = 7.7 mg	5 x 4 mg SFI	€ 23.72	€ 2.00	€ 5.53	€ 16.19	17.4	€ 112.68
Cimetidine 300 mg IV	10 x 200 mg AMP	€ 19.80	€ 2.00	€ 0.40	€ 17.40	17.4	€ 60.55
Appropriate comparator therapy							
Pemetrexed							
2 cycles (Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1))							
Dexamethasone [14] 2 x 4 mg	20 x 4 mg TAB	€ 24.61	€ 2.00	€ 1.05	€ 21.56	6	€ 21.56
Folic acid [15] 350 – 1.000 µg/day	30 x 400 µg SFI	€ 3.10	€ 0.00	€ 0.00	€ 3.10	70	€ 9.30 - € 15.50
Vitamin B12 [14] 1,000 µg/day, every 3 cycles	5 x 1,000 µg SFI	€ 4.49	€ 0.22	€ 0.20	€ 4.07	1	€ 4.07
17.4 cycles							
Dexamethasone [14] 2 x 4 mg	100 x 4 mg TAB	€ 79.54	€ 2.00	€ 5.40	€ 72.14	52.2	€ 75.31
Folic acid [15] 350 – 1,000 µg/day	30 x 400 µg SFI	€ 3.10	€ 0.00	€ 0.00	€ 3.10	365	€ 37.72 - € 75.43
Vitamin B12 [14] 1,000 µg/day, every 3 cycles	10 x 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.32	€ 6.71	5.8	€ 3.89

15 The cost calculation for folic acid is based on the single dose of 400 µg of the non-divisible tablets available for cost calculation related to a dose range of 400 - 800 µg per day, even if a dose range of 350 - 1000 µg is given in the product information.

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	Treatment days/ year	Costs/ patient/ year
Paclitaxel							
2 cycles *Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy* *(only for patients with ECOG-PS 0-1)*							
Dexamethasone [14] 2 x 20 mg	10 x 20 mg TAB	€ 32.42	€ 2.00	€ 0.00	€ 30.42	2	€ 30.42
Dimetindene IV 1 mg/10 kg = 7.7 mg	5 x 4 mg SFI	23.72	€ 2.00	€ 5.53	€ 16.19	2	€ 16.19
Cimetidine [14] 300 mg IV	10 x 200 mg AMP	€ 19.80	€ 2.00	€ 0.40	€ 17.40	2	€ 17.40
4 - 6 cycles *Atezolizumab + bevacizumab + paclitaxel + carboplatin* *(only for patients with ECOG PS 0-1 and non-squamous NSCLC)*							
Dexamethasone [14] 2 x 20 mg	10 x 20 mg TAB	€ 32.42	€ 2.00	€ 0.00	€ 30.42	4 - 6	€ 30.42 - € 52.09
	20 x 20 mg TAB	€ 54.09	€ 2.00	€ 0.00	€ 52.09		
Dimetindene IV 1 mg/10 kg = 7.7 mg	5 x 4 mg SFI	€ 23.72	€ 2.00	€ 5.53	€ 16.19	4 - 6	€ 32.82 - € 48.57
Cimetidine [14] 300 mg IV	10 x 200 mg AMP	€ 19.80	€ 2.00	€ 0.40	€ 17.40	4 - 6	€ 17.40 - € 34.80
17.4 cycles							
Dexamethasone [14] 2 x 20 mg	50 x 20 mg TAB	€ 118.88	€ 2.00	€ 0.00	€ 116.88	17.4	€ 81.35
Dimetindene IV 1 mg/10 kg = 7.7 mg	5 x 4 mg SFI	€ 23.72	€ 2.00	€ 5.53	€ 16.19	17.4	€ 112.68
Cimetidine [14] 300 mg IV	10 x 200 mg AMP	€ 19.80	€ 2.00	€ 0.40	€ 17.40	17.4	€ 60.55
Cisplatin							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Hydration and forced diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	2	€ 91.10

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	Treatment days/ year	Costs/ patient/ year
Sodium chloride 0.9% Inf. Solution, 3 - 4.4 l/day	6 x 1,000 ml INF	€ 25.09	€ 1.25	€ 2.05	€ 21.79	2	€ 21.79 - € 32.58
	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58		
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
Sodium chloride 0.9% Inf. Solution, 3 - 4.4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	17.4	€ 170.07 - € 263.11
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Abbreviations: INF = infusion solution; AMP = ampoules; SFI = solution for injection; TAB = tablets							

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 € 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 do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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 special agreement on contractual unit costs of retail pharmacist services (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 authorised 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 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 therapeutic indication, whereby the definition of a product class or group is based on the corresponding information 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.

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:

a) Adults with locally advanced or metastatic NSCLC expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

   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.

b) Adults with locally advanced or metastatic NSCLC expressing PD-L1- (in ≥ 1% to < 50% of tumour cells), with no EGFR, ALK or ROS1 aberrations; first-line therapy

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

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 November 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 13 April 2023.

On 20 April 2023 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 28 April 2023 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 July 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2023. The deadline for submitting statements was 22 August 2023.

The oral hearing was held on 11 September 2023.

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 10 October 2023, and the proposed resolution was approved.

At its session on 19 October 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 November 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	13 April 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	6 September 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 September 2023	Conduct of the oral hearing, if necessary: Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	20 September 2023 5 October 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	10 October 2023	Concluding discussion of the draft resolution
Plenum	19 October 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 19 October 2023

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

Prof. Hecken