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) and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Tremelimumab (new therapeutic indication: non-small cell lung cancer, EGFR/ALK-negative, first-line, combination with durvalumab and platinum-based chemotherapy)

of 5 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient tremelimumab on 1 April 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 30 March 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on the G-BA website (www.g-ba.de) on 3 July 2023, 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 tremelimumab compared with 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 tremelimumab.

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 Tremelimumab (Tremelimumab AstraZeneca) in accordance with the product information

Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising EGFR mutations or ALK positive mutations.

Therapeutic indication of the resolution (resolution of 05.10.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with metastatic NSCLC with PD-L1 expression ≥ 50% with no genomic EGFR or ALK tumour mutations, first-line therapy

Appropriate comparator therapy for tremelimumab in combination with durvalumab and 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)

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

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) <u>Adults with metastatic NSCLC with PD-L1 expression < 50% with no genomic EGFR or ALK tumour mutations, first-line therapy</u>

Appropriate comparator therapy for tremelimumab in combination with durvalumab and 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, RET or ROS1) at the time of therapy with tremelimumab in combination with durvalumab.

Molecularly stratified therapy for ALK translocations and EGFR mutations is already excluded by the therapeutic indication.

With regard to the authorisation status for first-line treatment of metastatic NSCLC with no sensitising EGFR mutations or ALK-positive mutations, the cytostatic agents cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, vinorelbine and the antibodies atezolizumab, bevacizumab, cemiplimab, ipilimumab, nivolumab, pembrolizumab and tremelimumab are available in general.

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:

- 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 Working Group for Thoracic Oncology in the Arbeitsgemeinschaft Internistische Onkologie in der Deutschen Krebsgesellschaft e.V. (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.

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.

For the present therapeutic indication, it is assumed that there is neither an indication for definitive chemoradiotherapy nor for definitive local therapy.

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 metastatic NSCLC with PD-L1 expression ≥ 50% with no genomic EGFR or ALK tumour mutations, first-line therapy

For first-line treatment of metastatic 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 written statements of the AkdÄ and the scientific-medical societies also name monotherapy with an ICI as the treatment standard. 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 therapy of nivolumab and ipilimumab and two cycles of platinum-based chemotherapy is also available as a treatment option regardless of histology.

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) Adults with metastatic NSCLC with PD-L1 expression < 50% with no genomic EGFR or ALK tumour mutations, first-line therapy

For first-line treatment of metastatic 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 therapy of nivolumab and ipilimumab and two cycles of platinum-based chemotherapy is available as a treatment option regardless of histology.

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 written statements of the scientific-medical societies, 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 tremelimumab is assessed as follows:

a) Adults with metastatic NSCLC with PD-L1 expression ≥ 50% with no genomic EGFR or ALK tumour mutations, first-line therapy

An additional benefit is not proven.

Justification:

In the absence of direct comparator studies of tremelimumab in combination with durvalumab and platinum-based chemotherapy versus the appropriate comparator therapy, the pharmaceutical company uses an adjusted indirect comparison according to the procedure of Bucher et al. for the proof of an additional benefit. For the adjusted indirect comparison via the bridge comparator of platinum-based chemotherapy, the pharmaceutical company includes the POSEIDON study on the side of tremelimumab in combination with durvalumab and platinum-based chemotherapy and the KEYNOTE024 and KEYNOTE042 studies on the side of pembrolizumab as monotherapy.

Description of the POSEIDON study

The POSEIDON study is an open-label randomised controlled phase III study comparing tremelimumab + durvalumab + platinum-based chemotherapy or durvalumab + platinum-based chemotherapy versus platinum-based chemotherapy. Adults with histologically or cytologically confirmed NSCLC (stage IV) with no EGFR mutation or ALK translocation whose tumours showed a PD-L1 expression were enrolled in the study. A prerequisite for enrolment in the study was an Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) ≤ 1. Patients were excluded if they had the option of curative surgery or radiotherapy or had received prior chemotherapy or other systemic therapies for metastatic NSCLC.

A total of 1,013 patients were stratified according to PD-L1 status (≥ 50%, < 50%), stage of the disease (IVA, IVB) and tumour histology (squamous, non-squamous) in a 1:1:1 ratio to either tremelimumab + durvalumab + platinum-based chemotherapy (N = 338), durvalumab + platinum-based chemotherapy (N = 338) or platinum-based chemotherapy (N = 337). For patient population a), only the tremelimumab + durvalumab + platinum-based chemotherapy vs platinum-based chemotherapy arms are relevant for the sub-population of patients with PD-L1 expression ≥ 50% (101 patients in the intervention arm and 97 patients in the comparator arm). An extension cohort in China was not considered in the benefit assessment.

In both the relevant intervention arm and the comparator arm, the patients were treated largely in accordance with the requirements in the product information or the Pharmaceuticals Directive (AM-RL) on off-label use (Annex VI to Section K). There were deviations with regard to the renewed administration of durvalumab as monotherapy - permitted according to the study protocol - followed by durvalumab in combination with tremelimumab (re-treatment) after disease progression.

In the comparator arm, platinum-based chemotherapy was administered for 4 to 6 cycles at the doctor's discretion. The treatment options for platinum-based chemotherapy in both arms for patients with non-squamous NSCLC were pemetrexed + cisplatin or pemetrexed +

carboplatin and for squamous NSCLC gemcitabine + cisplatin or gemcitabine + carboplatin. Regardless of the tumour histology, nab-paclitaxel + carboplatin could also be administered. Patient-individual selection was made by the principal investigator prior to randomisation. Pemetrexed maintenance treatment could be given at the doctor's discretion every 4 weeks in the intervention arm and every 3 or 4 weeks in the comparator arm from cycle 5 onwards in patients who received pemetrexed as chemotherapy and had no disease progression.

Treatment was given in both study arms until disease progression, unacceptable toxicity or the occurrence of another discontinuation criterion. Under certain conditions, treatment beyond disease progression was possible in the intervention arm, as already described (re-treatment).

Primary endpoints of the study were progression-free survival (PFS) and overall survival. Patient-relevant secondary endpoints were endpoints on morbidity, health-related quality of life, and adverse events (AEs).

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

- 1st data cut-off from 12.03.2021: pre-specified final analysis of overall survival, analyses on patient-reported endpoints of the morbidity and health-related quality of life categories
- 2nd data cut-off from 25.10.2021: analyses of AEs, discontinuation due to AEs and severe AEs (CTCAE grade ≥ 3)
- 3rd data cut-off from 11.03.2022: analyses of overall survival and SAEs

The pre-specified 1st data cut-off from 12.03.2021 is used for the benefit assessment. Based on the data from the dossier, it is unclear whether the two additional data cut-offs were planned in advance or what specific triggers there were for these subsequent data cut-offs. Also in the oral hearing, the pharmaceutical company does not provide any relevant information in this regard.

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.

For the benefit assessment, the 2nd interim analysis from 09.05.2016 is used.

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 relevant sub-population for the present assessment (patients with PD-L1 expression ≥ 50%) comprises 299 patients in the pembrolizumab arm and 300 patients in the comparator arm.

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.

For the benefit assessment, the 2nd interim analysis from 26.02.2018 is used.

For indirect comparison

A core requirement for the consideration of studies in the adjusted indirect comparison via a bridge comparator is similarity.

In terms of study design, patient population and bridge comparator, the POSEIDON as well as KEYNOTE-024 and KEYNOTE-042 studies are sufficiently similar.

With regard to the similarity of the patient populations of the POSEIDON as well as KEYNOTE-024 and KEYNOTE-042 studies, the demographic and clinical characteristics are sufficiently comparable. Differences can be seen with regard to the characteristic of descent, whereby the percentage of patients with a white descent in the POSEIDON study is significantly lower compared to the percentage in the KEYNOTE-024 study (approx. 50% vs approx. 80%). This is negligible because, as an approximation for this characteristic for the endpoint of overall survival, there are no relevant effect modifications for the region characteristic (Europe/North America vs rest of the world) in the POSEIDON study or skin colour (white vs non-white) in the KEYNOTE-024 study. There is no information on the KEYNOTE-042 study.

The POSEIDON, KEYNOTE-024 and KEYNOTE-042 studies differ with regard to the platinum-based chemotherapy used as a bridge comparator. In terms of the platinum component (carboplatin or cisplatin), carboplatin was used in approximately 80% of patients in the comparator arm of the POSEIDON study and in approximately 70% of patients in the KEYNOTE-024 study. Only carboplatin was administered in the KEYNOTE-042 study. In terms of the chemotherapy component, the majority of patients with non-squamous histology in the POSEIDON and KEYNOTE-024 studies received pemetrexed. Data for the relevant sub-population of the KEYNOTE-042 study are not available. Patients with squamous histology mainly received gemcitabine in addition to the platinum component in the POSEIDON and KEYNOTE-024 studies. In the POSEIDON study, approx. 5% of patients received nab-paclitaxel, regardless of histology, while in the KEYNOTE-024 study, paclitaxel was administered across all histologies (approx. 11%). Maintenance treatment with pemetrexed was planned in all 3 studies only for non-squamous histology. In the POSEIDON study, 56% of these patients received maintenance treatment with pemetrexed, whereas in the KEYNOTE-024 study only 37% did. Data for the relevant sub-population of the KEYNOTE-042 study are not available.

In summary, there are partial differences in study and patient characteristics as well as the chemotherapy component of the bridge comparator between the POSEIDON as well as KEYNOTE-024 and KEYNOTE-042 studies, none of which, however, fundamentally call into question the sufficient similarity to conduct an adjusted indirect comparison via the bridge comparator of platinum-based chemotherapy.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, the adjusted indirect comparison does not show any statistically significant difference between tremelimumab + durvalumab + platinum-based chemotherapy and pembrolizumab. This does not provide any hint for an additional benefit of tremelimumab + durvalumab + platinum-based chemotherapy compared to pembrolizumab, an additional benefit is therefore not proven.

Morbidity and quality of life

For the endpoints of the categories of morbidity and quality of life, no suitable data are available.

Against the background of an unequal representation of the burden of treatment over the course of the cycle in the study arms, the PRO data of the POSEIDON study are estimated to be unusable. Thus, no suitable data are available for the endpoints collected with the EORTC QLQ-C30, EORTC QLQ-LC13, the EQ-5D VAS and the PGIC on one edge of the indirect comparison.

Side effects

For the POSEIDON study, no data are available for the relevant sub-population for the predefined final data cut-off from 12.03.2021. Since the data on the total population for the endpoints of adverse events (AEs), serious adverse events (SAEs) and discontinuation due to AEs do not differ relevantly between this predefined data cut-off and the data cut-offs (25.10.2021 and 22.03.2022) submitted by the pharmaceutical company in the dossier, the data from the dossier are used. In contrast, for the endpoint of severe AEs (CTCAE grade ≥ 3), the information on the total population differs relevantly between the predefined final data cut-off from 12.03.2021 and the data cut-off from 25.10.2021 submitted by the pharmaceutical company, which is why no suitable data from the POSEIDON study are available for an indirect comparison for this endpoint. There are no data on the relevant sub-population for the KEYNOTE-042 study.

Total adverse events (AEs)

AEs occurred in almost all patients of the POSEIDON and KEYNOTE-024 studies sub-populations that are assessment-relevant for the indirect comparison.

Serious adverse events (SAE)

For the endpoint of SAEs, the adjusted indirect comparison does not show any statistically significant difference between tremelimumab + durvalumab + platinum-based chemotherapy and pembrolizumab.

Therapy discontinuation due to adverse events

For the endpoint of therapy discontinuation due to AEs, the open-label study design of both the POSEIDON and KEYNOTE-024 studies results in a high risk of bias, which is why the data are unsuitable for indirect comparison due to insufficient certainty of results.

PRO-CTCAE and immune-mediated AEs

No suitable data or none at all are available for the endpoints of PRO-CTCAE and immune-mediated AEs.

Overall, for the side effects, there is no hint for a higher or lower harm of tremelimumab + durvalumab in combination with platinum-based chemotherapy compared to pembrolizumab, thus a higher or lower harm is not proven.

Overall assessment/ conclusion

For the assessment of the additional benefit of durvalumab in combination with tremelimumab and platinum-based chemotherapy versus pembrolizumab in adults with metastatic NSCLC with PD-L1 expression ≥ 50% with no genomic EGFR or ALK tumour mutations, results are available from the adjusted indirect comparison of the POSEIDON study with the KEYNOTE-024 and KEYNOTE-042 studies on the bridge comparator of platinum-based chemotherapy. The studies presented are sufficiently similar and overall suitable for conducting an adjusted indirect comparison.

For the endpoint of overall survival, there is no relevant difference for the assessment.

No suitable data are available for the endpoint categories of morbidity and quality of life.

For the endpoint category of side effects, there are no relevant differences for the assessment of the endpoint of SAE. No suitable data are available for severe AEs (CTCAE ≥ 3) or therapy discontinuation due to AEs.

In the overall assessment, an additional benefit of tremelimumab in combination with durvalumab and platinum-based chemotherapy over pembrolizumab for adults with metastatic NSCLC with PD-L1 expression ≥ 50% with no genomic EGFR or ALK tumour mutations is not proven.

b) Adults with metastatic NSCLC with PD-L1 expression < 50% with no genomic EGFR or ALK tumour mutations, first-line therapy

An additional benefit is not proven.

Justification:

In the absence of direct comparator studies of tremelimumab in combination with durvalumab and platinum-based chemotherapy versus the appropriate comparator therapy, the pharmaceutical company uses an adjusted indirect comparison according to the procedure of Bucher et al. for the proof of an additional benefit also for patient population b). For the adjusted indirect comparison via the bridge comparator of platinum-based chemotherapy, the pharmaceutical company includes the POSEIDON study on the side of durvalumab in combination with tremelimumab and platinum-based chemotherapy and the CA209-9LA study on the side of nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy.

Description of the POSEIDON study

For a detailed description of the POSEIDON study, please refer to patient population a).

With regard to patient population b), the sub-population of patients with PD-L1 expression < 50% is relevant for the present benefit assessment (237 patients in the intervention arm and 240 patients in the comparator arm).

Description of the CA209-9LA study

The CA209-9LA study is an ongoing, open-label, randomised controlled phase III study comparing nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy with platinum-based combination chemotherapy, which started in 2017 and was conducted in 103 study sites in North and South America, Europe and Australia.

Adults with stage IV squamous and non-squamous NSCLC with no EGFR mutation or ALK translocation with an ECOG-PS ≤ 1 regardless of PD-L1 expression were enrolled, in addition 2% of patients were in stage IIIB with no option for curative therapy. Prior systemic therapy for stage IIIB and IV NSCLC was not allowed.

In total, 719 patients were randomised in a 1:1 ratio to treatment with nivolumab + ipilimumab + platinum-based chemotherapy (N = 361) or to treatment with platinum-based chemotherapy alone (N = 358), stratified by PD-L1 expression (≥ 1% vs < 1%), tumour histology (squamous histology vs non-squamous histology) and sex (male vs female). Data from an additional sub-study from China are not available. The sub-population of patients with PD-L1 expression < 50% (262 patients in the intervention arm and 235 patients in the comparator arm) is relevant for the present benefit assessment.

The treatment options were: Carboplatin in combination with paclitaxel for patients with squamous histology or either cisplatin or carboplatin in combination with pemetrexed for patients with non-squamous histology. The principal investigators selected the combination chemotherapy prior to randomisation.

The use of the study medication in both study arms complies with the requirements in the relevant product information or guidelines. The product information does not contain any details on the combination of paclitaxel or pemetrexed with carboplatin. The maximum treatment duration for nivolumab + ipilimumab is 24 months.

In the comparator arm, up to 4 cycles of chemotherapy were administered, after which patients with squamous histology and no disease progression could receive maintenance treatment with pemetrexed starting at cycle 5.

Treatment was given until disease progression, unacceptable intolerance, withdrawal of consent or reaching the maximum treatment duration.

The primary endpoint of the CA209-9LA study was overall survival. Patient-relevant secondary endpoints were assessed in the categories of morbidity and side effects.

For the benefit assessment, the a priori planned, final analysis for the data cut-off from 09.03.2020 is used.

Similarity of studies for indirect comparison

A core requirement for the consideration of studies in the adjusted indirect comparison is similarity.

Both POSEIDON and CA209-9LA studies have a very similar study design. The patient populations of the relevant sub-populations of the two studies are sufficiently similar with the exception of the descent characteristic.

In the POSEIDON study, the percentage of patients with a white descent is much lower compared to the percentage in the CA209-9LA study (approx. 60% vs approx. 80%). The percentage of Asian patients in the POSEIDON study was higher compared to the CA209-9LA study (31% vs 9%). This difference is relevant because a statistically significant effect modification with clear qualitative differences between the results for Asian and non-Asian patients was shown for the endpoint of overall survival in the POSEIDON study. In the CA209-9LA study, in contrast, there is no statistically significant effect modification for the descent characteristic.

From the point of view of the clinical experts within the framework of the written statement procedure, this difference between Asian and non-Asian patients is not reflected in the evidence.

Nevertheless, the descent characteristic represents a relevant effect modifier in the present data constellation, especially due to the qualitative effect modification in the POSEIDON study. Corresponding subgroup analyses to verify this point were not submitted by the pharmaceutical company.

In the overall assessment, there are therefore relevant differences between the two studies, which is why the indirect comparison submitted by the pharmaceutical company for patients with a PD-L1 expression < 50% is unsuitable for the benefit assessment.

Conclusion

For the assessment of the additional benefit of tremelimumab in combination with durvalumab and platinum-based chemotherapy versus nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy in adults with metastatic NSCLC with a PD-L1 expression < 50% with no genomic EGFR or ALK tumour mutations, results from the adjusted indirect comparison of the POSEIDON study with the CA209-9LA study on the bridge comparator of platinum-based chemotherapy are available in the dossier.

The data presented are unsuitable for an indirect comparison due to relevant differences in the patient populations of the two studies with regard to the descent characteristic, which represents a relevant, qualitative effect modifier for the endpoint of overall survival in the POSEIDON study, as well as the fact that no subgroup analyses were submitted by the pharmaceutical company to verify this point.

In the overall assessment, an additional benefit of tremelimumab in combination with durvalumab and platinum-based chemotherapy compared to the appropriate comparator therapy for adults with metastatic NSCLC with a PD-L1 expression < 50% with no genomic EGFR or ALK tumour mutations is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Tremelimumab AstraZeneca with the active ingredient tremelimumab.

The therapeutic indication assessed here is as follows:

"Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising EGFR mutations or ALK positive mutations."

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 metastatic NSCLC with PD-L1 expression ≥ 50% with no genomic EGFR or ALK tumour mutations, 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 metastatic NSCLC with PD-L1 expression < 50% with no genomic EGFR or ALK tumour mutations, 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 tremelimumab in combination with durvalumab and platinum-based chemotherapy (POSEIDON study) versus pembrolizumab (KEYNOTE0-24 and KEYNOTE-042 studies) via the bridge comparator of platinum-based chemotherapy for assessment. The studies presented are sufficiently similar and suitable for conducting an adjusted indirect comparison.

There is no relevant difference for the assessment of overall survival.

No suitable data are available for morbidity and quality of life.

For the side effects, there are no relevant differences for the assessment of the endpoint of SAE. No suitable data are available for severe AEs (CTCAE ≥ 3) or therapy discontinuation due to AEs.

In the overall assessment, an additional benefit of tremelimumab in combination with durvalumab and platinum-based chemotherapy over pembrolizumab for adults with metastatic NSCLC with PD-L1 expression ≥ 50% with no genomic EGFR or ALK tumour mutations is not proven.

Patient group b)

The pharmaceutical company submits an adjusted indirect comparison of tremelimumab in combination with durvalumab and platinum-based chemotherapy (POSEIDON study) versus nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (CA209-9LA study) for assessment.

The data presented are unsuitable for an indirect comparison due to relevant differences in the patient populations of the two studies with regard to the descent characteristic, which represents a relevant, qualitative effect modifier for the endpoint of overall survival in the POSEIDON study, as well as the fact that no subgroup analyses were submitted by the pharmaceutical company to verify this point.

In the overall assessment, an additional benefit of tremelimumab in combination with durvalumab and platinum-based chemotherapy compared to the appropriate comparator therapy for adults with metastatic NSCLC with a PD-L1 expression < 50% with no genomic EGFR or ALK tumour mutations 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) 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% (43,939 to 49,909 patients).
2. Of these, 46.63% of patients are in stage IV at initial diagnosis[2]. Of the remaining 53.37% of patients who are in stage I-IIIB, 37.7% will progress to stage IV in 2022[3]. The total number of patients is 29,330 to 33,315.
3. First-line therapy is given in 76.9% to 96.1% of cases (20,937 - 30,982 patients).
4. The percentage of patients with no EGFR mutation is 85.8% - 89.7 %[4,5]. The percentage of patients with no ALK translocation is 94.9% - 98.0%[Fehler! Textmarke nicht definiert.]. The percentage of patients with BRAF V600 mutation is 0.6% - 1.2%[6]. The percentage of patients with RET fusion is 0.6% - 0.9%[7]. The percentage of patients with no ROS translocation is 96.3% - 98.5%[Fehler! Textmarke nicht definiert.]. 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% (16,893 to 27,213 patients).
5. The percentage of patients with PD-L1 expression ≥ 50% of tumour cells is 25.9% to 28.9%[Fehler! Textmarke nicht definiert.] (4,375 to 7,756 patients) and PD-L1 expression < 50% of tumour cells is 71.1% to 74.1%[Fehler! Textmarke nicht definiert.] (12,011 to 20,165 patients).

2 Benefit assessment according to Section 35a SGB V, A23-29 | A23-31, durvalumab and tremelimumab (NSCLC), 29.06.2023

3 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)

4 Benefit assessment according to Section 35a SGB V, A21-86, osimertinib (NSCLC, adjuvant), 29.09.2021

5 Benefit assessment according to Section 35a SGB V, A21-98, cemiplimab (non-small cell lung cancer), 28.10.2021

6 2. Addendum to the benefit assessment according to Section 35a SGB V, A23-29 | A23-31, durvalumab and tremelimumab (NSCLC), 31.08.2023

7 Benefit assessment according to Section 35a SGB V, A21-27, selpercatinib (non-small cell lung cancer), 11.06.2021

6. Considering 88.3% of patients are insured by the SHI, there are 14,917 to 24,029 patients in the first-line therapy (PD-L1 expression ≥ 50%: 3,863 to 6,848 patients; PD-L1 expression < 50%: 10,606 to 17,806 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 product characteristics, SmPC) for Tremelimumab AstraZeneca (active ingredient: tremelimumab) at the following publicly accessible link (last access: 26 May 2023):

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

Treatment with durvalumab in combination with tremelimumab and platinum-based chemotherapy 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 card).

The training material contains, in particular, information and warnings about immune-mediated adverse reactions.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2023).

Tremelimumab is administered in combination with durvalumab and platinum-based chemotherapy every 3 weeks for 4 cycles, followed by durvalumab monotherapy and histology-based maintenance treatment with pemetrexed every 4 weeks including a fifth dose of tremelimumab in week 16.

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 days 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 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.

According to the product information, cisplatin is dosed differently depending on the concomitant active ingredient - in combination with pemetrexed, the product information specifies a dosage of 75 mg/m^2.

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 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.

Treatment period:

a) Adults with metastatic NSCLC with PD-L1 expression ≥ 50% with no genomic EGFR or ALK tumour mutations, 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				
Tremelimumab + durvalumab + platinum-based chemotherapy [8]				
Tremelimumab	1 x per 21-day cycle	4	1	4.0
Durvalumab	1 x per 21-day cycle	4	1	4.0
Carboplatin	1 x per 21-day cycle	4	1	4.0
Cisplatin	1 x per 21-day cycle	4	1	4.0
nab-paclitaxel	3 x per 21-day cycle	4	3	12.0
Gemcitabine	2 x per 21-day cycle	4	2	8.0

8 The treatment options for platinum-based chemotherapy were pemetrexed + cisplatin or pemetrexed + carboplatin for non-squamous NSCLC, gemcitabine + cisplatin or gemcitabine + carboplatin for squamous NSCLC, and nab-paclitaxel + carboplatin, regardless of tumour histology.

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	4	1	4.0
Antibody maintenance treatment and histology-based maintenance treatment with pemetrexed				
Tremelimumab	1 x in week 16	1	1	1.0
Durvalumab	1 x per 28-day cycle	10	1	10.0
Pemetrexed	1 x per 28-day cycle	10	1	10.0
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	1	13.0
Cemiplimab	1 x per 21-day cycle	17.4	1	17.4
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			

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	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[9]				
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
nab-paclitaxel	1 x per 21-day cycle	4 - 6	3	12.0 - 18.0
Maintenance treatment[9]				
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			

9 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
	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

b) Adults with metastatic NSCLC with PD-L1 expression < 50% with no genomic EGFR or ALK tumour mutations, 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				
Tremelimumab + durvalumab + platinum-based chemotherapy [8]				
Tremelimumab	1 x per 21-day cycle	4	1	4.0
Durvalumab	1 x per 21-day cycle	4	1	4.0
Carboplatin	1 x per 21-day cycle	4	1	4.0
Cisplatin	1 x per 21-day cycle	4	1	4.0

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	3	12.0
Gemcitabine	2 x per 21-day cycle	4	2	8.0
Pemetrexed	1 x per 21-day cycle	4	1	4.0
Antibody maintenance treatment and histology-based maintenance treatment with pemetrexed				
Tremelimumab	1 x in week 16	1	1	1.0
Durvalumab	1 x per 28-day cycle	10	1	10.0
Pemetrexed	1 x per 28-day cycle	10	1	10.0
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	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
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			

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	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[9]				
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
nab-paclitaxel	3 x per 21-day cycle	4 - 6	3	12.0 - 18.0
Maintenance treatment[9]				
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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	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 (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).[10]

a) Adults with metastatic NSCLC with PD-L1 expression ≥ 50% with no genomic EGFR or ALK tumour mutations, 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					
Tremelimumab + durvalumab + platinum-based chemotherapy[8]					
Tremelimumab	75 mg	75 mg	3 x 25 mg	4.0	12 x 25 mg
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	4.0	12 x 500 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 1 x 450 mg	4.0	4.0 x 600 mg + 4.0 x 450 mg
Cisplatin	75 mg/m2 = 142.5 mg	142.5 mg	1 x 50 mg + 1 x 100 mg	4.0	4.0 x 50 mg + 4.0 x 100 mg
nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 x 100 mg	12.0	24.0 x 100 mg
Gemcitabine	1,250 mg/m² = 2,375 mg	2375 mg	2 x 200 mg + 2 x 1,000 mg	8.0	16.0 x 200 mg + 16.0 x 1,000 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	4.0	8.0 x 500 mg
Antibody maintenance treatment and histology-based maintenance treatment with pemetrexed					
Tremelimumab	75 mg	75 mg	3 x 25 mg	1.0	3.0 x 25 mg
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	10.0	30 x 500 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	10.0	20 x 500 mg

[10] 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
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/m^2 = 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/m^2 = 950 mg	950 mg	2 x 500 mg	2.0	4 x 500 mg
Paclitaxel	175 mg/m^2 = 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 (only for patients with ECOG PS 0-1 and non-squamous NSCLC)					
Induction 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
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[9]					
Atezolizumab	840 mg	840 mg	1 x 840 mg	20.1 –	22.1 x 840 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
				22.1	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				
	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 +

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					6.0 x 450 mg
nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 x 100 mg	12 – 18	24 x 100 mg – 36 x 100 mg
Maintenance[9]					
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				
	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/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
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
nab-paclitaxel	100 mg/m² = 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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
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
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

b) Adults with metastatic NSCLC with PD-L1 expression < 50% with no genomic EGFR or ALK tumour mutations, 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					
Tremelimumab + durvalumab + platinum-based chemotherapy [8]					
Tremelimumab	75 mg	75 mg	3 x 25 mg	4.0	12 x 25 mg
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	4.0	12 x 500 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 1 x 450 mg	4.0	4.0 x 600 mg + 4.0 x 450 mg
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 50 mg + 1 x 100 mg	4.0	4.0 x 50 mg + 4.0 x 100 mg
nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 x 100 mg	12.0	24.0 x 100 mg
Gemcitabine	1,250 mg/m² = 2,375 mg	2375 mg	2 x 200 mg + 2 x 1,000 mg	8.0	16.0 x 200 mg + 16.0 x 1,000 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	4.0	8.0 x 500 mg
Antibody maintenance treatment and histology-based maintenance treatment with pemetrexed					
Tremelimumab	75 mg	75 mg	3 x 25 mg	1.0	3.0 x 25 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
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	10.0	30 x 500 mg
Pemetrexed	500 mg/m^2 = 950 mg	950 mg	2 x 500 mg	10.0	20 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/m^2 = 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/m^2 = 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/m^2 = 950 mg	950 mg	2 x 500 mg	2.0	4 x 500 mg
Paclitaxel	175 mg/m^2 = 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 (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	4.0 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
				– 6.0	– 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[9]					
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
	or				
	1,680 mg	1,680 mg	2 x 840 mg	9 – 7	18.0 x 840 mg – 14.0 x 840 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
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[9]					
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					

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 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
nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 x 100 mg	52.2	104.4 x 100 mg
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	2375 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.

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					
Tremelimumab 25 mg	1 CIS	€ 2,329.58	€ 2.00	€ 222.43	€ 2,105.15
Durvalumab 500 mg	1 CIS	€ 2,167.38	€ 2.00	€ 206.55	€ 1,958.83
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
nab-paclitaxel 100 mg	1 PIS	€ 429.36	€ 2.00	€ 19.84	€ 407.52
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
Pemetrexed 500 mg	1 CIS	€ 572.68	€ 2.00	€ 26.64	€ 544.04
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 100 mg	1 CIS	€ 289.47	€ 2.00	€ 13.20	€ 274.27
Paclitaxel 150 mg	1 CIS	€ 428.97	€ 2.00	€ 19.82	€ 407.15
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 CIS	€ 572.68	€ 2.00	€ 26.64	€ 544.04
Vinorelbine 50 mg	1 CIS	€ 1,424.56	€ 2.00	€ 67.07	€ 1,355.49
Vinorelbine 10 mg	1 CIS	€ 294.01	€ 2.00	€ 13.42	€ 278.59
Abbreviations: CIS = 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					

LAUER-TAXE® last revised: 15 September 2023

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 5a SGB 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							
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	4	€ 91.10
Sodium chloride 0.9% infusion solution, 3 l - 4.4 l/day	6 x 1,000 ml INF	€ 25.09	€ 1.25	€ 2.05	€ 21.79	4	€ 65.16
	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58		
Pemetrexed							
4 cycles of 21 days each *(Tremelimumab + durvalumab + platinum-based chemotherapy)*							

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
Dexamethasone [11] 2 x 4 mg	100 x 4 mg TAB	€ 79.54	€ 2.00	€ 5.40	€ 72.14	12	€ 17.31
Folic acid [12] 350 – 1,000 µg/day	30 x 400 µg TAB	€ 3.10	€ 0.00	€ 0.00	€ 3.10	84	€ 8.68 - € 17.36
Vitamin B12[11] 1,000 µg/day, every 3 cycles	10 x 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.32	€ 6.71	2	€ 1.34
10 cycles of 28 days each (Antibody maintenance treatment and histology-based maintenance treatment with pemetrexed)							
Dexamethasone [11] 2 x 4 mg	100 x 4 mg TAB	€ 79.54	€ 2.00	€ 5.40	€ 72.14	30	€ 43.28
Folic acid[12] 350 - 1,000 µg/day	30 x 400 µg TAB	€ 3.10	€ 0.00	€ 0.00	€ 3.10	281	€ 29.04 - € 58.07
Vitamin B12[11] 1,000 µg/day, every 3 cycles	10 x 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.32	€ 6.71	3	€ 2.01
Appropriate comparator therapy							
Pemetrexed							
2 cycles (Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0-1))							
Dexamethasone [11] 2 x 4 mg	20 x 4 mg TAB	€ 24.61	€ 2.00	€ 1.05	€ 21.56	6	€ 21.56
Folic acid[12] 350 - 1,000 µg/day	30 x 400 µg TAB	€ 3.10	€ 0.00	€ 0.00	€ 3.10	70	€ 9.30 - € 15.50
Vitamin B12[11] 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							

11 Fixed reimbursement rate

12 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 - 1,000 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
Dexamethasone [11] 2 x 4 mg	100 x 4 mg TAB	€ 79.54	€ 2.00	€ 5.40	€ 72.14	52.2	€ 75.31
Folic acid[12] 350 – 1,000 µg/day	30 x 400 µg TAB	€ 3.10	€ 0.00	€ 0.00	€ 3.10	365	€ 37.72 - € 75.43
Vitamin B12[11] 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							
2 cycles *Nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy* *(only for patients with ECOG-PS 0-1)*							
Dexamethasone [11] 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[11] 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 [11] 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[11] 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 [11] 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[11] 300 mg IV	10 x 200 mg AMP	€ 19.80	€ 2.00	€ 0.40	€ 17.40	17.4	€ 60.55

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
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
Sodium chloride 0.9% infusion solution, 3 - 4.4 l/day	6 x 1,000 ml INF	€ 25.09	€ 1.25	€ 2.05	€ 21.79	2	€ 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% infusion 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		

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 approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

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

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called indetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

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 SGBV.

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 metastatic NSCLC with PD-L1 expression ≥ 50% with no genomic EGFR or ALK tumour mutations, first-line therapy

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product: "Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising EGFR mutations or ALK positive mutations."

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:
Product information for tremelimumab (Tremelimumab AstraZeneca); product information for Tremelimumab AstraZeneca 20 mg/ml concentrate for the preparation of an infusion solution; last revised: February 2023

b) Adults with metastatic NSCLC with PD-L1 expression < 50% with no genomic EGFR or ALK tumour mutations, first-line therapy

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product: "Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with

metastatic non-small cell lung cancer (NSCLC) with no sensitising EGFR mutations or ALK positive mutations."

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:

Product information for tremelimumab (Tremelimumab AstraZeneca); product information for Tremelimumab AstraZeneca 20 mg/ml concentrate for the preparation of an infusion solution; last revised: February 2023

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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 21 February 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 March 2023, the pharmaceutical company submitted a dossier for the benefit assessment of tremelimumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 March 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 tremelimumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 June 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 July 2023. The deadline for submitting statements was 24 July 2023.

The oral hearing was held on 7 August 2023.

By letter dated 9 August 2023, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by the IQWiG was submitted to the G-BA on 31 August 2023 and 15 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 26 September 2023, and the proposed resolution was approved.

At its session on 5 October 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	21 February 2023	Determination of the appropriate comparator therapy
Working group Section 35a	2 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 August 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	6 September 2023 20 September 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	26 September 2023	Concluding discussion of the draft resolution
Plenum	5 October 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 5 October 2023

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

Prof. Hecken