Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Atezolizumab (new therapeutic indication: non-small cell lung cancer, PD-L1 expression ≥ 50% on TC or ≥ 10% on IC, EGFR/ALK-negative, first-line)

of 19 November 2021

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies 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 benefits,
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 statutory health insurance funds,
6. requirements for a quality-assured application.

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

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

2. Key points of the resolution

The active ingredient atezolizumab (Tecentriq) was listed for the first time on 1 October 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 30 April 2021, atezolizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2a letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of amendments to the terms of marketing authorisations for

medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 19 May 2021, i.e. no later than four weeks after the pharmaceutical company has been notified of the authorisation for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient atezolizumab with the new therapeutic indication "Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% tumour cells (TC) or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 September 2021, thus initiating the written statement procedure. An erratum of IQWiG's benefit assessment (version 2.0) was published on 10 September 2021. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of atezolizumab, compared to the appropriate comparator therapy, could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. 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 atezolizumab.

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 atezolizumab (Tecentriq) in accordance with the product information

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% tumour cells (TC) or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC.

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

Therapeutic indication of the resolution (resolution from 19.11.2021):

see new therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression ≥ 50% of the tumour cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

Appropriate comparator therapy:

- Pembrolizumab as monotherapy

b) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

Appropriate comparator therapy:

- Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))

  or

- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceuticals Directive

  or

- Carboplatin in combination with nab-paclitaxel

  or

- Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for adults with non-squamous histology)

  or

- Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for adults with squamous histology)

  or

- Monotherapy with gemcitabine or vinorelbine (only for adults with ECOG performance status 2 as an alternative to platinum-based combination treatment)

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

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

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

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

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

on 1. Besides atezolizumab, the following active ingredients are approved for the present therapeutic indication: bevacizumab, cemiplimab, cisplatin, crizotinib, dabrafenib, docetaxel, entrectinib, gemcitabine, ifosfamide, ipilimumab, mitomycin, nivolumab, paclitaxel, nab-paclitaxel, pembrolizumab, pemetrexed, trametinib, vindesine, vinorelbine

on 2. For the present therapeutic indication, it is assumed that the patients have no indication for definitive local therapy. A non-medicinal treatment cannot be considered as a comparator therapy in this therapeutic indication. This does not affect the implementation of radiotherapy or surgery as a palliative treatment option.

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

- Nivolumab: Resolution of 3 June 2021
- Ipilimumab: Resolution of 3 June 2021
- Entrectinib (ROS1-positive NSCLC): Resolution of 18 February 2021
- Atezolizumab: Resolutions of 2 April 2020
- Pembrolizumab: Resolutions of 19 September 2019
- Pembrolizumab (PD-L1 expression: TPS ≥ 50%): Resolution of 3 August 2017

- Dabrafenib (NSCLC with BRAF V600-mutation): Resolution of 19 October 2017
- Trametinib (NSCLC with BRAF V600-mutation): Resolution of 19 October 2017
- Crizotinib (ROS1-positive NSCLC): Resolution of 16 March 2017

Guidelines:

Section K of the Pharmaceuticals Directive, Annex VI - Off-label use, resolution of 18 October 2018: Carboplatin-containing medicinal products for advanced non-small cell lung cancer (NSCLC) - combination therapy

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

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

In first-line treatment, based on the available evidence on treatment options and depending on PD-L1 expression, it is differentiated into two sub-populations with a PD-L1 expression cut-off value of 50% of the tumour cells (or a Tumour Proportion Score [TPS] of 50%):

a) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression ≥ 50% of the tumour cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

Current guidelines recommend pembrolizumab monotherapy for first-line treatment of metastatic NSCLC when PD-L1 expression is ≥ 50%, regardless of histologic status. The corresponding benefit assessment of pembrolizumab, based on the KEYNOTE-024 study, showed an indication of a considerable additional benefit compared with platinum-based chemotherapy (resolution of 3 August 2017). Pembrolizumab significantly improved overall survival, delayed the onset of significant disease symptoms and severe adverse events (CTCAE grade ≥ 3) and showed beneficial effects on health-related quality of life. Therefore, pembrolizumab monotherapy represents a current therapy standard and is determined as an appropriate comparator therapy. Pembrolizumab is approved only for metastatic NSCLC with a PD-L1 expression of ≥ 50% of the tumour cells or a TPS ≥ 50%.

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

additional benefit was determined, the extent of which cannot be quantified. Based on these data, the combination therapy of pembrolizumab and platinum-containing chemotherapy is currently not considered an appropriate comparator therapy for the present patient population.

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

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

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

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

b) <u>Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line</u>

Specific recommendations for patients who have PD-L1 expression on ≥ 10% of tumour-infiltrating immune cells are not currently included in the available evidence. Therefore,

those therapy options that are eligible for the unselected patient population in this regard will also be considered as appropriate comparator therapy for adults with PD-L1 expression on ≥ 10% of tumour-infiltrating immune cells.

For patients with PD-L1 expression < 50% of the tumour cells or a TPS < 50%, platinum-based combination chemotherapy (cis- or carboplatin) with a third-generation cytostatic agent (vinorelbine, gemcitabine, docetaxel, paclitaxel, or pemetrexed) is a therapy standard according to the available evidence. However, no preference for a particular combination can be inferred from the evidence. In contrast to cisplatin, carboplatin is not approved for the treatment of NSCLC, but can be prescribed as "off-label use" for patients (see Annex VI to Section K of the Pharmaceuticals Directive), whereby the selection of the platinum component should be based on the different toxicity profile and existing comorbidities of the patients. Nab-paclitaxel is approved in combination with carboplatin for the first-line treatment of NSCLC. In the guidelines, this combination is recommended in the present therapeutic indication, therefore the G-BA classifies carboplatin in combination with nab-paclitaxel as a further appropriate therapy option for patients with a PD-L1 expression of < 50% of the tumour cells or a TPS < 50%.

For pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy, a hint of non-quantifiable additional benefit for adults with a PD-L1 expression of < 50% of the tumour cells or a TPS < 50% was declared by resolution of the G-BA on 19 September 2019, based on a meta-analysis of the two randomised controlled trials, Keynote-021G and Keynote-189. Compared to pemetrexed plus platinum-containing chemotherapy, there was a benefit in the endpoint on overall survival, the extent of which was non-quantifiable due to available subgroup analyses and their relevant uncertainties. In determining the present appropriate comparator therapy, it is taken into account that a meta-analysis of two randomised controlled trials forms the data basis for this sub-population. Furthermore, clinical experts stated in the benefit assessments for atezolizumab (resolution of 2 April 2020) that pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy represents another therapy standard of care. Therefore, the G-BA also considers this therapy option to be another appropriate therapy option in the present therapeutic indication for patients with non-squamous histology and a PD-L1 expression < 50% of the tumour cells or a TPS < 50%.

For pembrolizumab in combination with carboplatin and nab-paclitaxel, a hint of considerable additional benefit for squamous NSCLC in patients with PD-L1 expression < 50% of the tumour cells or a TPS < 50% was declared by resolution dated 19 September 2019. Based on the KEYNOTE 407 study, there was an advantage in the endpoint on overall survival. Currently, the guidelines identified in the search and synopsis of evidence do not yet provide a clear or unanimous recommendation for the use of the aforementioned combination therapy. However, in view of the positive

treatment effects of the combination of pembrolizumab and carboplatin and either paclitaxel or nab-paclitaxel presented in the benefit assessment resolution, it is currently considered an appropriate comparator therapy (only in the case of squamous histology) for patients with PD-L1 expression < 50% of the tumour cells or a TPS < 50%.

For atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, no additional benefit was declared in the benefit assessment by resolution of 2 April 2020 compared with the appropriate comparator therapy for the first-line treatment of metastatic non-squamous NSCLC in patients with a PD-L1 expression of < 50% of the tumour cells or a TPS < 50%, as there were no usable data for a comparison with the appropriate comparator therapy. This combination therapy is therefore not assessed as an appropriate comparator therapy.

For atezolizumab in combination with nab-paclitaxel and carboplatin, no additional benefit over nab-paclitaxel and carboplatin for the first-line treatment of metastatic non-squamous NSCLC in patients with PD-L1 expression of < 50% of the tumour cells or a TPS < 50% was declared in the benefit assessment resolution of 2 April 2020. Overall, there were no statistically significant differences for the endpoint categories overall survival, morbidity and quality of life. The disadvantages in severe AE (CTCAE grade 3-4) were considered significant for patients. Atezolizumab in combination with nab-paclitaxel is therefore not considered an appropriate comparator therapy.

For the combination therapy nivolumab, ipilimumab and two cycles of platinum-based chemotherapy, the G-BA, in its resolution of 3 June 2021, identified an indication of a minor additional benefit for patients with a PD-L1 expression of < 50% of the tumour cells or a TPS < 50%. There was a benefit in overall survival, which was assessed as a significant improvement in benefit over platinum-based chemotherapy. In contrast, relevant disadvantages were found in the side effect endpoints, which were rated as significant and burdensome for the patients. In a weighing decision, the negative effects in side effects did not call into question the additional benefit due to the improvement in overall survival, but they did lead to a downgrading of the extent of additional benefit. This combination therapy is not currently considered an appropriate comparator therapy as nivolumab in combination with ipilimumab and two cycles of platinum-based chemotherapy is a fairly new treatment option whose therapeutic value cannot yet be conclusively assessed.

There are no clear recommendations in the guidelines for patients with a deteriorated general condition (ECOG performance status (PS) 2). Taking into account patient-individual criteria, it should be weighed here against the background of the toxicity profile of a platinum-based combination chemotherapy versus the expected benefit. In this regard, monotherapy with gemcitabine or vinorelbine is considered appropriate as an alternative to combination chemotherapy for patients with ECOG-PS 2.

In the overall assessment, the G-BA determined the combination and monotherapies listed above as equally appropriate comparator therapies for the patient group, whose tumours show PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells, taking into account the corresponding additional information in brackets.

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with metastatic, non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression ≥ 50% of the tumour cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

An additional benefit is not proven.

Justification:

For the benefit assessment on patient population a), the pharmaceutical company submits an adjusted indirect comparison of atezolizumab versus the appropriate comparator therapy pembrolizumab according to Bucher. For the indirect comparison, the pharmaceutical company includes the IMpower110 study (atezolizumab versus platinum-based chemotherapy) and the KEYNOTE 024 and KEYNOTE 042 studies (pembrolizumab versus platinum-based chemotherapy). The studies are randomised, open-label phase III studies. The pharmaceutical company does not use the extension study KEYNOTE-042-China for the adjusted indirect comparison due to missing information on patient characteristics for the relevant sub-population.

IMPower110 study

The IMPower110 study included adults with histologically or cytologically confirmed stage IV NSCLC without EGFR mutations or ALK translocations, whose tumours showed PD-L1 expression and who have not previously received systemic therapy for the metastatic stage.

A total of 572 patients were randomised in a 1:1 ratio to the two study arms (N= 285 atezolizumab; N= 287 platinum-based chemotherapy). Randomisation was stratified by sex, histology, ECOG performance status (PS), and PD-L1 expression in tumour tissue (determined by means of immunohistochemistry (IHC) of the tumour cells (TC) and tumour-infiltrating immune cells (IC)).

Adults with non-squamous NSCLC received either pemetrexed + cisplatin or pemetrexed + carboplatin in the comparator arm of the IMPower110 study. Adults with squamous NSCLC received gemcitabine + cisplatin or gemcitabine + carboplatin. The active ingredients were administered according to the respective product information or the Pharmaceuticals Directive (AM-RL) for off-label use (Annex VI to Section K). Whether patients received four or

six cycles of chemotherapy was determined by the principal investigator prior to randomisation. Following platinum-based chemotherapy, patients with non-squamous histology received maintenance treatment with pemetrexed, provided the four to six cycles of platinum-based chemotherapy were completed and no progression occurred. Patients with squamous histology received best supportive care (BSC). Treatment with atezolizumab or maintenance treatment with pemetrexed in the comparator arm was given until disease progression, unacceptable side effects, or death. Switching patients from the comparison to the intervention arm was not allowed in the IMPower110 study.

The ongoing study was conducted in 144 centres across South and North America, Europe and Asia. The primary endpoint of the study is overall survival. In addition, data on morbidity, health-related quality of life and side effects were collected. The pre-specified interim data cut-off from 10 September 2018 will be used for the benefit assessment.

On the relevant sub-population of the IMPower110 study

For the assessment of the present patient population, only patients in the IMPower110 study who have PD-L1 expression ≥ 50% of the tumour cells or a tumour proportion score [TPS] ≥ 50% are relevant.

The basis for the inclusion of patients in the IMPower110 study was the determination of PD-L1 expression with the SP142 test (Ventana PD-L1 Assay). Accordingly, the approved therapeutic indication for atezolizumab is based on data from a sub-population of the study with high PD-L1 expression as determined by the SP142 test (counting according to tumour cell and immune cell score (TC and IC)). In addition, the IMPower110 study assessed tumour tissue PD-L1 expression with additional tests, including the 22C3 test (Dako Commercial Ready Assay) in 534 of 554 included adults (96%; counting according to tumour proportion score (TPS)).

In the pembrolizumab studies (KEYNOTE 042 and KEYNOTE 024) included in the adjusted indirect comparison, PD-L1 expression was assessed with the 22C3 test.

It is clear from the available evidence and the statements of the scientific-medical societies in the present benefit assessment procedure that the different test systems for determining PD-L1 expression identify different, incongruent patient populations with high PD-L1 expression. However, according to the marketing authorisation of atezolizumab and pembrolizumab as monotherapy, no specific test for the determination of PD-L1 expression is required, only the use of a validated test. Accordingly, the specific test system (e.g. 22C3, SP142) is not relevant for the question of the benefit assessment according to Section 35a SGB V, provided that a validated test was used for the determination of PD-L1 expression according to the marketing authorisation. The counting of cells according to the tumour proportion score (TPS) and the tumour cell score (TC) is identical. Therefore, high PD-L1 expression according to TPS and TC is considered equivalent in the benefit assessment.

To ensure better comparability of the studies in the indirect comparison, the pharmaceutical company uses the 22C3 test to form the relevant sub-population of the IMPower110 study.

The review of the SP142 and 22C3 tests showed only moderate concordance between them, thus representing uncertainty for the IMPower110 study. The sub-population of the IMPower110 study included in the indirect comparison corresponds only to 58% of the patient population for which the present marketing authorisation of atezolizumab was granted. In its dossier, however, the pharmaceutical company was able to show that the effects for the endpoint on overall survival in the IMPower110 study were almost identical between the population to be granted marketing authorisation and the patient population used for the adjusted indirect comparison. Therefore, the sub-population of the IMPower110 study submitted by the pharmaceutical company is used for the adjusted indirect comparison.

KEYNOTE 024 study

The KEYNOTE 024 study included adults with histologically or cytologically confirmed stage IV NSCLC without EGFR mutations or ALK translocations, whose tumours showed PD-L1 expression ≥ 50% and who have not previously received systemic therapy for the metastatic stage. PD-L1 expression was assessed using the 22C3 test (Dako Commercial Ready Assay).

A total of 305 patients were randomised to the two study arms in a 1:1 ratio (N= 154 pembrolizumab, N= 151 platinum-based chemotherapy). Randomisation was stratified by histology, geographic region, and ECOG PS.

The treatment administered in the comparator arm was determined by the principal investigator prior to randomisation. The choices were pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, or paclitaxel + carboplatin. The combination with pemetrexed was only considered for adults with non-squamous histology. The active ingredients were administered according to the respective product information or the Pharmaceuticals Directive (AM-RL) for off-label use (Annex VI to Section K). The maximum treatment duration for pembrolizumab was 35 cycles. Platinum-based chemotherapy was used for four to six cycles. Adults with non-squamous histology could receive maintenance treatment with pemetrexed. After disease progression, patients were allowed to switch from the comparator arm to pembrolizumab in the KEYNOTE 024 study.

The study, conducted in 142 centres across Oceania, Europe, Asia and North America, was completed in 2016. The primary endpoint was progression-free survival. In addition, overall survival, morbidity, health-related quality of life and side effects were recorded as secondary endpoints. The data cut-off of the second interim analysis of 9 May 2016 is used for the indirect comparison. The entire study population of the KEYNOTE 024 study is relevant for the present indirect comparison since the study exclusively includes patients with PD-L1 expression ≥ 50% of the tumour cells.

KEYNOTE 042 study

The KEYNOTE 042 study included patients with histologically or cytologically confirmed diagnosis of NSCLC whose tumours expressed PD-L1 ≥ 1% and were in locally advanced or metastatic stage. Prior systemic therapy for the metastatic stage was not allowed. PD-L1 expression was assessed using the 22C3 test (Dako Commercial Ready Assay).

A total of 1274 patients were randomised in a 1:1 ratio to the two study arms (N= 637 pembrolizumab; N= 637 platinum-based chemotherapy). Randomisation was stratified by ECOG PS, histology, PD-L1 expression, and geographic region.

The treatment administered in the comparator arm was determined by the principal investigator prior to randomisation. The options were pemetrexed + carboplatin or paclitaxel + carboplatin, with pemetrexed only being considered for patients with non-squamous histology. The active ingredients were administered according to the respective product information or the Pharmaceuticals Directive (AM-RL) for off-label use (Annex VI to Section K). The maximum treatment duration for pembrolizumab was 35 cycles. Carboplatin was used for four to six cycles. After at least four cycles of platinum-based chemotherapy, maintenance treatment with pemetrexed was recommended for adults with non-squamous histology. A change of patients from the comparator arm to the intervention arm was not planned in the study.

The ongoing study is being conducted in 196 centres across South America, Europe, Asia, South Africa and Canada. The primary endpoint of the study is overall survival. Adverse events will be collected as patient-relevant secondary endpoints. Data from the second interim analysis of 26 February 2018 will be used for the indirect comparison. The relevant sub-population of the KEYNOTE 042 study for the adjusted indirect comparison are patients with PD-L1 expression ≥ 50% of the tumour cells.

<u>On the similarity of the IMPower110, KEYNOTE 024 and KEYNOTE 042 studies in an indirect comparison</u>

Based on the available information, the patient populations are considered to be sufficiently comparable between the IMPower110, KEYNOTE 024 and KEYNOTE 042 studies as well as between the treatment arms in each of the studies.

With regard to the bridge comparator "platinum-based chemotherapy", there are differences between the studies in terms of the specific active ingredients of platinum-based chemotherapy and the specifications on the patient group (squamous/non-squamous) to be subject to the individual active ingredients or combination therapies. According to the information provided by the pharmaceutical company in its written statement, maintenance treatment with pemetrexed was administered to 39.8% of the patients in the relevant sub-population of the IMPower110 study. In the KEYNOTE 024 study, 37% of adult patients received maintenance treatment with pemetrexed. No data for the relevant sub-population are available for the KEYNOTE 042 study. Overall, the differences or lack of data for the bridge comparator "platinum-based chemotherapy" do not call into question the similarity of the studies for the indirect comparison, but are taken into account when interpreting the results on the side effect endpoints.

Due to a lack of data, the similarity of the studies in terms of treatment and observation duration cannot be examined.

Information on subsequent therapies was not available for the IMPower110 study in the dossier. In its written statement, the pharmaceutical company stated that the percentage of patients with a subsequent therapy in the relevant sub-population for the indirect comparison, analogous to the population to be granted marketing authorisation, is about 30%. In the KEYNOTE 024 study, the percentage of adults with subsequent therapy was 22.7% and 16.6%, respectively. For the KEYNOTE 042 study, no data are available on the percentage of subsequent therapies for the relevant sub-population. Therefore, the similarity of the studies regarding subsequent therapies cannot be assessed due to a lack of data.

In summary, however, the similarity assumption for the indirect comparison is not rejected.

On the homogeneity assumption

As only one study is available for atezolizumab, it is not possible to investigate homogeneity. Regarding the studies on pembrolizumab, no significant heterogeneity was observed when considering the endpoint on overall survival.

In the overall assessment, the adjusted indirect comparison presented is used for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

The overall survival was defined in the studies as the time from randomisation to death from any cause. For the endpoint on overall survival, the adjusted indirect comparison shows no statistically significant difference between the treatment groups.

Morbidity

In the IMPower110 study, in the endpoint category of morbidity, the endpoints on health status were assessed using the EQ-5D visual analogue scale (VAS) while symptomatology using the EORTC QLQ-C30 and LC-13 questionnaires. For these endpoints, the pharmaceutical company did not submit data for the relevant sub-population of the IMPower110 study for the adjusted indirect comparison.

Thus, no usable data for an adjusted indirect comparison are available for the endpoint category of morbidity.

Quality of life

Health-related quality of life was assessed in the IMPower110 study using the EORTC QLQ-C30 questionnaire. For this endpoint, the pharmaceutical company did not submit data for the relevant sub-population of the IMPower110 study for the adjusted indirect comparison.

Thus, no usable data for an adjusted indirect comparison are available for the endpoint category of health-related quality of life.

Side effects

Adverse events (AEs; in total)

In the IMPower110 and KEYNOTE 024 studies, adverse events (AEs) occurred in nearly all study participants. Data from the KEYNOTE 042 study are not available. The results were only presented additionally.

Serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3)

For the endpoints serious adverse events (SAE) and severe AEs (CTCAE grade ≥ 3), the adjusted indirect comparison showed no statistically significant differences between the treatment arms.

Therapy discontinuation due to AEs

For the endpoint on discontinuation of therapy due to AEs, the adjusted indirect comparison shows a statistically significant difference in favour of atezolizumab.

The present effect in the endpoint "treatment discontinuation due to AEs" is prone to large uncertainties. On the one hand, this is due to the different periods of time during which the KEYNOTE 024 and IMPower110 studies were conducted. During the oral hearing in the present benefit assessment procedure, scientific-medical societies stated that the management of immune checkpoint inhibitor-mediated side effects has improved since the KEYNOTE 024 study was conducted. Accordingly, it is unclear to what extent AEs that led to treatment discontinuation in the pembrolizumab study would also have resulted in treatment discontinuation at the time of the IMPower110 study. On the other hand, uncertainties arise due to the existing differences in the bridge comparator "platinum-based chemotherapy" with regard to the specific active ingredients of platinum-based chemotherapy and the specifications on the patient group (squamous/non-squamous) to be subject to the individual active ingredients or combination therapies. Further uncertainties in the interpretation of the effect are due to the low event numbers or rates of treatment discontinuation due to AEs in the atezolizumab and pembrolizumab arms of the respective study, as well as the open-label study design against the background of the subjective assessment of the endpoint.

Taking into account the uncertainties described above, the effect in the endpoint "discontinuation of therapy due to AEs" is not assessed as being sufficient to derive an additional benefit in the endpoint category of side effects.

With its written statement, the pharmaceutical company presents a further adjusted indirect comparison for the endpoint on discontinuation due to AEs, including a meta-analysis of the KEYNOTE 024 and KEYNOTE 042 studies. However, the meta-analysis refers exclusively to patients with non-squamous NSCLC, although data from the KEYNOTE 042 study on patients with squamous NSCLC are also available from previous benefit assessment procedure. Since the meta-analysis did not fully consider all relevant data, the additional, adjusted indirect

comparison presented in the written statement is not used for the endpoint on discontinuation of therapy due to AEs.

Immune-mediated AEs

In the dossier, the pharmaceutical company did not provide data for the endpoint on immune-mediated AEs for the relevant sub-population of the IMPower110 study for the indirect comparison. With its written statement, the pharmaceutical company submits data for the relevant sub-population of the IMPower110 study for the indirect comparison. However, the pharmaceutical company states that an indirect comparison is not feasible due to the different operationalisation of the endpoint "immune-mediated AEs" in the respective studies on atezolizumab and pembrolizumab. The data on immune-mediated AEs are not considered usable.

Overall assessment / conclusion

For the assessment of the additional benefit of atezolizumab for the first-line treatment of adult patients with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression ≥ 50% of the tumour cells or a tumour proportion score [TPS] ≥ 50% and who do not have EGFR mutant or ALK-positive NSCLC, results are available for overall survival and side effects compared with the appropriate comparator therapy with pembrolizumab.

This assessment is based on an adjusted indirect comparison of the IMPower110 (atezolizumab versus platinum-based chemotherapy) and KEYNOTE 024 and KEYNOTE 042 (pembrolizumab versus platinum-based chemotherapy) studies according to Bucher.

For the endpoint on overall survival, no statistically significant difference was detected between the treatment arms.

There are no usable data from the adjusted indirect comparison for the endpoint categories of morbidity and health-related quality of life.

In the endpoint category on side effects, there was no statistically significant difference between treatment arms for the endpoints serious adverse events (SAE) and severe AE (CTCAE grade ≥ 3). For the endpoint on treatment discontinuation due to AEs, there is a statistically significant difference in favour of atezolizumab between the treatment arms. However, this effect is prone to too much uncertainty and is not assessed as being sufficient to derive an additional benefit with regard to side effects.

In the overall analysis of the available results on patient-relevant endpoints from the adjusted indirect comparison, no relevant improvement of the therapy-relevant benefit can be determined.

As a result, the G-BA thus concludes that an additional benefit is not proven for atezolizumab as monotherapy for the treatment of adults with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% of the tumour cells and who do not have EGFR mutant or ALK-positive NSCLC.

b) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

An additional benefit is not proven.

Justification:

No data are available to allow an assessment of the additional benefit.

In its dossier, the pharmaceutical company does not consider patient population b) and accordingly does not present any data for the assessment of the additional benefit.

With its written statement, the pharmaceutical company submits data for the present patient population. However, these could have been submitted in a regular way in the dossier, and therefore, the data submitted during the written statement procedure are not used for the present assessment.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient atezolizumab (Tecentriq). The therapeutic indication assessed here is as follows: "Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% tumour cells (TC) or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC."

In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adults with metastatic, non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression ≥ 50% of the tumour cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

b) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

Patient group a)

For this patient group, results on overall survival and side effects of atezolizumab versus the appropriate comparator therapy pembrolizumab are available.

The assessment is based on an adjusted indirect comparison of the IMPower110 (atezolizumab versus platinum-based chemotherapy), and KEYNOTE 024 and KEYNOTE 042 (pembrolizumab versus platinum-based chemotherapy) studies, according to Bucher.

For the endpoint on overall survival, no statistically significant difference was detected between the treatment arms.

In the endpoint category of side effects, there was no statistically significant difference for serious AEs and severe AEs (CTCAE grade ≥ 3). For the endpoint on treatment discontinuation due to AEs, there is a statistically significant difference in favour of atezolizumab between the treatment arms. However, this effect is prone to too much uncertainty and is not assessed as being sufficient to derive an additional benefit with regard to side effects.

As a result, the G-BA states that an additional benefit is not proven.

Patient group b)

For this patient group, no data are available for the assessment of the additional benefit.

An additional benefit is not proven.

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

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

In order to allow consistent consideration of patient numbers, taking into account the resolutions made on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication of non-small cell lung cancer, the incidence of 62,380 patients forecast by the Robert Koch Institute for 2020 is used for the present calculation. This differs insignificantly from the incidence of 62,583 patients forecast by the pharmaceutical company for 2021. In addition, the incidence alone is used as the basis for the calculations, as these are patients in first-line therapy, and it is therefore unlikely that the existing patients have not yet received first-line treatment in previous years.

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

1. The percentage of lung cancer patients with NSCLC is 80.3 - 82% (50,091 - 51,152 patients).
2. Of these, 49.2% of patients are in stage IV (24,645 - 25,167 patients)
3. First-line therapy is given in 76.9 - 78.5% of cases (18,952 - 19,756 patients).
4. The percentage of patients without EGFR mutation is 85.8% - 89.7%[2,3]. The percentage of patients without ALK translocation is 94.9% - 98.0%[3]. In total, the number is 15,431 - 17,367 patients without EGFR mutation or ALK translocation.
5. The percentage of patients with PD-L1 high-expressing tumours (PD-L1 expression ≥ 50% of the tumour cells or tumour proportion score [TPS] ≥ 50%) was 28.9% (4,460 - 5,019 patients). Accordingly, the percentage of patients with PD-L1 expression < 50%

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

of the tumour cells or a TPS < 50% was 71.1% (10,972 - 12,348 patients). PD-L1 expression of ≥ 10% of the immune cells was seen in 6% of patients[4] (658 - 741 patients).

6. Taking into account a percentage of patients insured by the SHI of 88.3%, this results in:
   a) 3,940 - 4,430 patients with PD-L1 expression ≥ 50% of the tumour cells or a tumour proportion score [TPS] ≥ 50%
   b) 580 - 650 patients with a PD-L1 expression < 50% of the tumour cells or a TPS < 50% and a PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells

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

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Tecentriq (active ingredient: atezolizumab) at the following publicly accessible link (last access: 2 September 2021):

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

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

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

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

- training material for health professionals
- patient pass

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

[4] Kowanetz et al. Differential regulation of PD-L1 expression by immune and tumour cells in NSCLC and the response to treatment with atezolizumab (anti-PD-L1), Proc Natl Acad Sci U S A. 23 October 2018; 115(43): E10119–E10126.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 November 2021).

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

The recommended dosage for atezolizumab as monotherapy is either 840 mg every two weeks or 1,200 mg every three weeks, or 1,680 mg every four weeks. All therapy regimens listed according to the product information are taken into account for the cost calculation.

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

Cisplatin is dosed differently, depending on the concomitant medicinal product. According to the product information of the concomitant medicinal products, the single dose of cisplatin in combination with vinorelbine or gemcitabine is 75 - 100 mg/m², in combination with docetaxel and pemetrexed 75 mg/m² and in combination with paclitaxel 80 mg/m².

For carboplatin, a cycle duration of 3 weeks is used. For the use of carboplatin in the off-label indication "combination therapy for advanced NSCLC", Annex VI of the Pharmaceuticals Directive specifies the following dosage: up to 500 mg/m² or AUC 6.0. For the use of carboplatin in combination with nab-paclitaxel, a dosage of 500 mf/m² is also used, according to the product information.

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

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Atezolizumab	1 x per 14 day cycle	26.1 cycles	1	26.1
	or			
	1 x per 21 day cycle	17.4 cycles	1	17.4
	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	13 cycles	1	13
Appropriate comparator therapy				
a) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression ≥ 50% of the tumour cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line				
Pembrolizumab	1 x per 21 day cycle	17.4 cycles	1	17.4
	or			
	1 x per 42 day cycle	8.7 cycles	1	8.7
b) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line				
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))				
Cisplatin	1 x per 21 day cycle	17.4 cycles	1	17.4
Docetaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Gemcitabine	2 x per 21 day cycle	17.4 cycles	2	34.8
Paclitaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Pemetrexed	1 x per 21 day cycle	17.4 cycles	1	17.4
Vinorelbine	2 x per 21 day cycle	17.4 cycles	2	34.8
Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceuticals Directive				
Carboplatin	1 x per 21 day cycle	17.4 cycles	1	17.4
Docetaxel	1 x per 21 day cycle	17.4 cycles	1	17.4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Gemcitabine	2 x per 21 day cycle	17.4 cycles	2	34.8
Paclitaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
Pemetrexed	1 x per 21 day cycle	17.4 cycles	1	17.4
Vinorelbine	2 x per 21 day cycle	17.4 cycles	2	34.8
Carboplatin in combination with nab-paclitaxel				
Carboplatin	1 x per 21 day cycle	17.4 cycles	1	17.4
nab-paclitaxel	3 x per 21 day cycle	17.4 cycles	3	52.2
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for adults with non-squamous histology)				
Pembrolizumab	1 x per 21 day cycle	17.4 cycles	1	17.4
Pemetrexed	1 x per 21 day cycle	17.4 cycles	1	17.4
Carboplatin	1 x per 21 day cycle	17.4 cycles	1	17.4
Cisplatin	1 x per 21 day cycle	17.4 cycles	1	17.4
Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for adults with squamous histology)				
Pembrolizumab	1 x per 21 day cycle	17.4 cycles	1	17.4
Carboplatin	1 x per 21 day cycle	17.4 cycles	1	17.4
Paclitaxel	1 x per 21 day cycle	17.4 cycles	1	17.4
nab-paclitaxel	3 x per 21 day cycle	17.4 cycles	3	52.2
Monotherapy with gemcitabine or vinorelbine (only for adults with ECOG performance status 2 as an alternative to platinum-based combination regimen)				
Gemcitabine	3 x per 28 day cycle	13 cycles	3	39

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Vinorelbine	1 x per 7 day cycle	52.1 cycles	1	52.1

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 from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average 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)[5].

[5]Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
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	26 x 840 mg
Appropriate comparator therapy					
a) Adults with metastatic, non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression ≥ 50% of the tumour cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line					
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
b) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line					
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))					
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg
	80 mg/m² = 152 mg	152 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg + 17.4 x 10 mg
	100 mg/m² = 190 mg	190 mg	2 x 100 mg	17.4	34.8 x 100 mg
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Gemcitabine	1,250 mg/m² = 2,375 mg	2,375 mg	1 x 2,000 mg + 2 x 200 mg	34.8	34.8 x 2,000 mg + 69.6 x 200 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 + 1 x 150 mg	17.4	17.4 x 150 mg + 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
Vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 x 50 mg	34.8	34.8 x 50 mg
	30 mg/m² = 57 mg	57 mg	1 x 50 mg + 1 x 10 mg	34.8	34.8 x 50 mg + 34.8 x 10 mg
Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceuticals Directive					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 2 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 34.8 x 150 mg + 17.4 x 50 mg
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Gemcitabine	1,250 mg/m² = 2,375 mg	2375 mg	1 x 2,000 mg + 2 x 200 mg	34.8	34.8 x 2,000 mg + 69.6 x 200 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 + 1 x 150 mg	17.4	17.4 x 150 mg + 34.8 x 100 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 x 50 mg	34.8	34.8 x 50 mg
	30 mg/m² = 57 mg	57 mg	1 x 50 mg + 1 x 10 mg	34.8	34.8 x 50 mg + 34.8 x 10 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 2 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 34.8 x 150 mg + 17.4 x 50 mg
nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 x 100 mg	52.2	104.4 x 100 mg
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for adults with non-squamous histology)					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
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	1 x 600 mg	17.4	17.4 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
	= 950 mg		+ 2 x 150 mg + 1 x 50 mg		+ 34.8 x 150 mg + 17.4 x 50 mg
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg
Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for adults with squamous histology)					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 2 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 34.8 x 150 mg + 17.4 x 50 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 + 1 x 150 mg	17.4	17.4 x 150 mg + 34.8 x 100 mg
nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 x 100 mg	52.2	104.4 x 100 mg
Monotherapy with gemcitabine or vinorelbine (only for adults with ECOG performance status 2 as an alternative to platinum-based combination treatment)					
Gemcitabine	1,000 mg/m² = 1,900 mg	1,900 mg	1 x 2,000 mg	39	39 x 2,000 mg
Vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 x 50 mg	52.1	52.1 x 50 mg
	30 mg/m² = 57 mg	57 mg	1 x 50 mg +1 x 10 mg	52.1	52.1 x 50 mg +52.1 x 10 mg

Costs:

Costs of the medicinal products:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

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					
Atezolizumab 840 mg	1 CIS	€ 2,907.48	€ 1.77	€ 162.77	€ 2,742.94
Atezolizumab 1,200 mg	1 CIS	€ 4,128.95	€ 1.77	€ 232.53	€ 3,894.65
Appropriate comparator therapy					
Carboplatin 50 mg	5 ml INF	€ 34.38	€ 1.77	€ 1.11	€ 31.50
Carboplatin 150 mg	15 ml INF	€ 82.79	€ 1.77	€ 3.40	€ 77.62
Carboplatin 600 mg	60 ml INF	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Cisplatin 10 mg	10 ml CIS	€ 17.26	€ 1.77	€ 0.30	€ 15.19
Cisplatin 50 mg	50 ml CIS	€ 47.43	€ 1.77	€ 1.73	€ 43.93
Cisplatin 100 mg	100 ml CIS	€ 76.31	€ 1.77	€ 3.10	€ 71.44
Docetaxel 160 mg	8 ml CIS	€ 1,397.36	€ 1.77	€ 175.44	€ 1,220.15
Gemcitabine 200 mg	2 ml CIS	€ 28.57	€ 1.77	€ 0.83	€ 25.97
Gemcitabine 2,000 mg	20 ml CIS	€ 193.96	€ 1.77	€ 8.68	€ 183.51
nab-paclitaxel 100 mg	1 PIS	€ 429.09	€ 1.77	€ 52.91	€ 374.41
Paclitaxel 100 mg	1 CIS	€ 303.80	€ 1.77	€ 13.89	€ 288.14
Paclitaxel 150 mg	1 CIS	€ 450.59	€ 1.77	€ 20.86	€ 427.96
Pembrolizumab 100 mg	4 ml CIS	€ 3,037.06	€ 1.77	€ 170.17	€ 2,865.12
Pemetrexed 500 mg	1 PIC	€ 279.25	€ 1.77	€ 12.73	€ 264.75
Vinorelbine 10 mg	10 x 1 ml CIS	€ 293.74	€ 1.77	€ 13.42	€ 278.55
Vinorelbine 50 mg	10 x 5 ml CIS	€ 1,424.29	€ 1.77	€ 67.07	€ 1,355.45
Abbreviations: CIS = concentrate for the preparation of an infusion solution, INF = infusion solution, PIC = powder for the preparation of an infusion solution concentrate, PIS = powder for the preparation of an infusion suspension					

LAUER-TAXE® last revised: 1 November 2021

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 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 to the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, these non-prescription medicinal products are subject to a medicinal product dispensing price - significant to the insured - 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.

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
Appropriate comparator therapy							
Cisplatin							
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.							
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
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		€ 263.11
Paclitaxel							
Dexamethasone 20 mg[6]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84	17.4	€ 81.32
Dimetindene IV 1 mg/10 kg	5 x 4 mg SFI	€ 18.62	€ 1.77	€ 1.90	€ 14.95	17.4	€ 104.05
Cimetidin 300 mg IV[6]	10 CIS x 200 mg	€ 21.55	€ 1.77	€ 0.00	€ 19.78	17.4	€ 68.83

6 Fixed reimbursement rate

Designation of the therapy	Packaging size	Cost (pharmacy discount price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Pemetrexed							
Dexamethasone 2 x 4 mg[6]	100 TAB 4 mg	€ 79.27	€ 1.77	€ 5.40	€ 72.10	52.2	€ 75.27
Folic acid: 350 – 1,000 µg/day[7]	100 x 400 µg TAB	€ 16.21	€ 0.81	€ 2.36	€ 13.04	365	€ 47.60 - € 95.19
Vitamin B12[6] 1,000 µg/day, every 3 cycles	10 x 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.33	€ 6.70	5.8	€ 3.89
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; INF = infusion solution; TAB = tablets							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs 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 Hilfstaxe.

[7] 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.

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 24 March 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 19 May 2021, the pharmaceutical company submitted a dossier for the benefit assessment of atezolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 21 May 2021, in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient atezolizumab.

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

On 10 September 2021, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 2.0 dated 10 September 2021 replaces version 1.0 of the dossier assessment dated 1 September 2021. Due to the changes in version 2.0, the assessment result was influenced to the extent that a statement on the additional benefit for patient population b) was also described with the erratum.

The oral hearing was held on 11 October 2021.

By letter dated 12 October 2021, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by IQWiG was submitted to the G-BA on 29 October 2021.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 9 November 2021, and the proposed resolution was approved.

At its session on 19 November 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	24 March 2020	Determination of the appropriate comparator therapy
Working group Section 35a	6 October 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	11 October 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	20 October 2021 3 November 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	9 November 2021	Concluding discussion of the draft resolution
Plenum	19 November 2021	Adoption of the resolution on the amendment of Annex XII AM-RL (Pharmaceuticals Directive)

Berlin, 19 November 2021

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

Prof. Hecken