Justification

Gemeinsamer Bundesausschuss

to 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: NSCLC, Non-Squamous, First Line, Combination with Bevacizumab, Paclitaxel, and Carboplatin)

of 2 April 2020

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 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 15 October 2017 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 5 March 2019, Tecentriq received marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 13 November 2018, the pharmaceutical company filed an application to consolidate the evaluation procedures for atezolizumab according to Section 35a, paragraph 5b SGB V. At its session on 20 December 2018, the G-BA approved the application for consolidation in accordance with Section 35a, paragraph 5b SGB V.

On 24 September 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient atezolizumab with the new therapeutic indication “Tecentriq, in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In

patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated only after failure of appropriate targeted therapies." in due time.

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 2 January 2020, 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 atezolizumab 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. 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 arrived at 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, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated only after failure of appropriate targeted therapies.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin was determined as follows:

a) Adults with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line therapy

   Pembrolizumab as monotherapy

b) Adults with metastatic non-squamous non-small cell lung cancer; and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression); first-line therapy; or a EGFR mutant or ALK-positive NSCLC independent of the tumour proportion score [TPS] after pre-treatment with an appropriate targeted therapy.

   - Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed), taking into account the authorisation status.

     or

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

- Carboplatin in combination with a third-generation cytostatic agent (only for patients with an increased risk of cisplatin-induced side effects as part of a combination therapy; *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 patients without EGFR or ALK positive tumour mutations)

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 according to 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 Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. In terms of the authorisation status, the active ingredients cisplatin, docetaxel, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, vinorelbine, crizotinib, dabrafenib, trametinib, bevacizumab, and pembrolizumab are generally available for the first-line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC).

According to the present therapeutic indication, patients with activating EGFR mutations or ALK-positive NSCLC should already have received appropriate targeted therapy prior to therapy with atezolizumab. These tyrosine kinase inhibitors have therefore not been included.

On 2. For the present therapeutic indication, it is assumed that the patients do not have an indication for definitive local therapy.

Non-medicinal treatment is therefore not considered. The implementation of surgery or radiotherapy as a palliative therapy option remains unaffected.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:
- Pembrolizumab: (combination therapy): Resolution 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-positives NSCLC): Resolution of 16 March 2017

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

On 4. Taking into account the evidence available and the approved therapeutic indication of pembrolizumab, the G-BA differentiates patients in the present therapeutic indication into two sub-populations based on PD-L1 expression with a separation value of 50% (TPS).

Sub-population b) also includes different patient groups: Wild type patients with a PD-L1 expression < 50% as well as patients with an EGFR mutation or ALK translocation (each independent of PD-L1 expression) who have already received one or more corresponding targeted lines of therapy.

a) <u>Adults with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line therapy</u>

Current guidelines recommend a monotherapy with pembrolizumab for the first-line treatment of metastatic non-small cell lung cancer with a PD-L1 expression of ≥ 50%. The benefit assessment of pembrolizumab as monotherapy based on data from 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 and delayed the occurrence of severe AE. There are also beneficial effects for health-related quality of life; significant disease symptoms occurred later. Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy was evaluated by the G-BA in its resolution of 19 September 2019 for the patient group with a PD-L1 expression of ≥ 50% (TPS) based on an adjusted indirect comparison to pembrolizumab monotherapy. Because the extent of the additional benefit observed in the overall survival endpoint cannot be quantified for the entire sub-population and an assessment of symptomatology and health-related quality of life is not possible, an additional benefit is identified; however, the extent of this is non-quantifiable. On the basis of this data, the G-BA defines pembrolizumab as monotherapy as the only appropriate comparator therapy for the first-line treatment of patients with PD-L1 expression ≥ 50% (TPS).

b) <u>Adults with metastatic non-squamous non-small cell lung cancer; and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression); first-line therapy; or a EGFR mutant or ALK-positive NSCLC independent of the tumour proportion score [TPS] after pre-treatment with an appropriate targeted therapy</u>

According to the evidence available, platinum-based combination chemotherapy (cis- or carboplatin) with a third-generation cytostatic drug (vinorelbine, gemcitabine, docetaxel, paclitaxel, or pemetrexed) represents a therapeutic standard for patients with a PD-L1 expression < 50%. However, no preference for a particular combination can be deduced from the evidence.

Carboplatin, unlike cisplatin, is not approved for the treatment of NSCLC. However, it may be prescribed as “off-label use” for patients (see Annex VI to Section K of the Pharmaceuticals Directive); the selection of the platinum component should be based on the different toxicity profiles and existing patient comorbidities.

Within the scope of the benefit assessment, for pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy, a hint for a non-quantifiable additional benefit was issued in the resolution of 19 September 2019. For patients with a PD-L1 expression of < 50% (TPS), a hint for a non-quantifiable additional benefit compared with pemetrexed plus platinum-containing chemotherapy was found based on a meta-analysis of the two randomised and controlled Keynote-021G and Keynote-189 studies. An advantage was shown in the overall survival endpoint. However, the extent of this was non-quantifiable because of the subgroup analyses available and their relevant uncertainties. When 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, in the written comments on the present benefit assessment, clinical experts stated that pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy represents a further standard of care. The G-BA therefore considers this therapeutic option to be another useful therapeutic option in the present therapeutic indication.

Nab-paclitaxel in combination with carboplatin is approved for the first-line treatment of NSCLC. The guidelines recommend this combination in the present therapeutic indication; the G-BA therefore classifies nab-paclitaxel as another appropriate therapeutic option in the present therapeutic indication.

Bevacizumab is not included in the established appropriate comparator therapy. Guidelines describe bevacizumab (in addition to platinum-containing chemotherapy) only as a possible treatment option for selected patients. The higher risk of side effects is offset by an unclear prolongation of overall survival. Based on the evidence available, bevacizumab does not represent a standard therapy in the planned therapeutic indication.

Based on guidelines and systematic reviews, it can be concluded that patients with EGFR-mutated or ALK-positive NSCLC should primarily exhaust the targeted therapy options available (i.e. tyrosine kinase inhibitors). There are no treatment recommendations for subsequent (chemotherapeutic) first-line treatment based on high-quality evidence. Taking into account that a targeted therapy with a tyrosine kinase inhibitor differs significantly from the pharmacological approach of chemotherapy, according to current guidelines, in principle all approved therapy options that are also available to non-pretreated patients without activating mutations can be considered.

Because atezolizumab is used in combination with bevacizumab, paclitaxel, and carboplatin according to the present therapeutic indication, monochemotherapies such as gemcitabine or vinorelbine cannot be considered as appropriate comparator therapies. The target population for treatment with the combination therapy of four active ingredients is predominantly patients who are in good general condition.

Therefore, for a patients with a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) as well as for patients with EGFR-mutated or ALK-positive NSCLC after pretreatment with an appropriate targeted therapy, the G-BA has determined cisplatin or carboplatin in combination with a third generation cytostatic agent or pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients without EGFR or ALK positive tumour mutations) to be equally appropriate comparator therapies.

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

Change of the appropriate comparator therapy:

Compared with the original definition of the appropriate comparator therapy, for sub-population b), this is supplemented by pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy.

The amendment takes into account the resolution on pembrolizumab of 19 September 2019 and the importance of pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy in health care as expressed in the opinions of medical societies and experts.

This change in the appropriate comparator therapy neither effects the present assessment of additional benefit nor does it require a re-assessment of the benefit assessment.

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-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line therapy

For the treatment of adults with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line therapy, an additional benefit is not proven.

Justification:

The pharmaceutical company does not provide data for the assessment of the additional benefit because no suitable studies for comparison with the appropriate comparator therapy was identified. It is not possible to assess the additional benefit based on this data basis. Thus, an additional benefit is not proven.

b) Adults with metastatic non-squamous non-small cell lung cancer; and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression); first-line therapy; or a EGFR mutant or ALK-positive NSCLC independent of the tumour proportion score [TPS] after pre-treatment with an appropriate targeted therapy

For the treatment of adults with metastatic non-squamous non-small cell lung cancer; and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression); first-line therapy; or a EGFR mutant or ALK-positive NSCLC independent of the tumour proportion score [TPS] after pre-treatment with an appropriate targeted therapy, an additional benefit is not proven.

Justification:

To prove an additional benefit of atezolizumab, the pharmaceutical company presents a direct comparison of the two arms of the IMpower150 study. The IMpower150 study is an ongoing, randomised, controlled, open parallel group study. The study was initiated in March 2015 and includes three groups with a total of 1202 patients. According to the enrolment criteria, the study examined adults with stage IV metastatic, non-squamous NSCLC. Enrolment was independent of PD-L1 expression and EGFR or ALK tumour mutation; however, the expression or mutation status should be known. Only patients with an Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) of ≤ 1 were enrolled. The study is being conducted in 26 countries worldwide.

In the IMpower150 study, PD-L1 expression in tumour tissue was determined by the proportion of PD-L1 positive tumour cells (TC) and PD-L1 positive immune cells (IC). A PD-L1 expression of TC0/1/2 and IC0/1/2 is considered by the pharmaceutical company to be an approximation of a Tumour Proportion Score (TPS) < 50%. Complementary to this, a PD-L1 expression of TC3 or IC3 is evaluated by the pharmaceutical company to be an approximation of a PD-L1 expression ≥ 50% in accordance with TPS. It is viewed critically that a comprehensible and sound justification of the extent to which, in particular, a PD-L1 expression of IC3 actually corresponds to an approximation to a TPS ≥ 50% was not submitted by the pharmaceutical company.

For the benefit assessment, the pharmaceutical company compared the atezolizumab + paclitaxel + carboplatin + bevacizumab group with the paclitaxel + carboplatin + bevacizumab group in a direct comparison. The comparison with paclitaxel + carboplatin + bevacizumab does not correspond to the appropriate comparator therapy defined by the G-BA, which is not adequately implemented here. Consequently, the direct comparison is not used for the benefit assessment.

Furthermore, the pharmaceutical company presents data from study E4599. Study E4599 is a randomised, controlled, open parallel group study comparing paclitaxel + carboplatin with bevacizumab + paclitaxel + carboplatin. According to the enrolment criteria, adults with a non-squamous NSCLC who have had advanced, metastatic, or relapsed disease should be included. Only patients with an ECOG-PS ≤ 1 were enrolled. Previous systemic chemotherapy was not allowed. The study was conducted from 2001 to 2005 in Puerto Rico, South Africa and the US. The PD-L1 expression as well as the EGFR and ALK mutation status are unknown.

To prove an additional benefit, the pharmaceutical company presents an adjusted indirect comparison with carboplatin + paclitaxel from study E4599 via the bridge comparator bevacizumab + paclitaxel + carboplatin from the IMpower150 study. The adjusted indirect comparison presented is not usable.

On one hand, this assessment is based on differences in the care of the NSCLC. There is a period of about 12 years between the most recent data cut-offs of the two studies. During this time, there have been significant changes and innovations in the care of NSCLC. This is reflected in different pre- and follow-up therapies, among other things.

An enrolment criterion for the IMpower150 study was that patients with an EGFR mutation or ALK translocation were enrolled only after failure of a prior corresponding targeted therapy. These targeted previous therapies were not available to patients of study E4599. Thus, for study E4599 study, the proportion of patients with EGFR- or ALK-mutated tumours who would have been eligible for a targeted therapy prior to enrolment remains unclear. The situation is similar for the follow-up therapies. Thus, in the Impower150 study, 35% of patients with immunotherapy and 9% of patients without EGFR- or ALK-positive tumour mutations were treated with a targeted follow-up therapy. These treatment options were not yet available for patients in study E4599.

Furthermore, the patient characteristics of the two studies are not considered to be sufficiently similar. Only patients with non-squamous NSCLC were enrolled in the IMpower150 study included only patients with non-squamous NSCLC; this was not an enrolment criterion for the study E4599. In study E4599, only the proven squamous carcinoma was explicitly excluded. Furthermore, information on other characteristics such as smoker status, time since diagnosis of the disease, tumour size at the start of study, and concomitant treatments is missing in in thestudy E4599.

In summary, the IMpower150 study and the study E4599 cannot be considered sufficiently similar. The adjusted indirect comparison submitted by the pharmaceutical company is therefore not usable. On this data basis, it is not possible to evaluate an additional benefit for atezolizumab + bevacizumab + paclitaxel + carboplatin compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication of the medicinal product Tecentriq with the active ingredient atezolizumab. Tecentriq, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq in combination with bevacizumab, paclitaxel, and carboplatin is indicated only after failure of appropriate targeted therapies.

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

a) Adults with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line therapy

b) Adults with metastatic non-squamous non-small cell lung cancer; and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression); first-line therapy; or a EGFR mutant or ALK-positive NSCLC independent of the tumour proportion score [TPS] after pre-treatment with an appropriate targeted therapy

About patient group a)

The appropriate comparator therapy was determined by the G-BA as follows:

Pembrolizumab as monotherapy

The pharmaceutical company does not provide data for the assessment of the additional benefit compared with the appropriate comparator therapy. It is not possible to assess the additional benefit based on this data basis. Thus, an additional benefit is not proven.

About patient group b)

The appropriate comparator therapy was determined by the G-BA as follows:

- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed), taking into account the authorisation status.

  or

- Carboplatin in combination with a third-generation cytostatic agent (only for patients with an increased risk of cisplatin-induced side effects as part of a combination therapy; *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 patients without EGFR or ALK positive tumour mutations)

For the benefit assessment, the pharmaceutical company presents data from the ongoing, randomised, controlled, open Impower150 parallel group study. According to the enrolment criteria, the study examined adults with stage IV metastatic, non-squamous NSCLC. Furthermore, the randomised, controlled, open parallel group study E4599 comparing paclitaxel + carboplatin with bevacizumab + paclitaxel + carboplatin is presented. According to the enrolment criteria, adults with a non-squamous NSCLC who have had advanced, metastatic, or relapsed disease should be included.

In the IMpower150 study a direct comparison of atezolizumab + paclitaxel + carboplatin + bevacizumab with paclitaxel + carboplatin + bevacizumab is performed; however, this does not correspond to the defined appropriate comparator therapy, which excludes bevacizumab. The direct comparison is not used for the benefit assessment.

Furthermore, an adjusted indirect comparison with carboplatin + paclitaxel from the study E4599 via the bridge comparator bevacizumab + paclitaxel + carboplatin from the IMpower150 study is presented. Because of the different time periods of the studies and the resulting differences in the care of NSCLC in the historical course and the insufficiently similar patient characteristics between the two studies as well as uncertainties regarding other factors, the adjusted indirect comparison is not usable. Thus, an additional benefit is not proven.

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

In order to enable a consistent consideration of the number of patients taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication (pembrolizumab: 19 September 2019; osimertinib: 17 January 2019; alectinib: 21 June 2018; ceritinib: 1 February 2018), the G-BA uses the following derivation of patient numbers:

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 incidence for 2019 estimated at 56,979 patients from the justification of the benefit assessment of pembrolizumab (D-447, resolution of the G-BA of 19 September 2019, dossier assessment of the IQWiG: A19-30) is used as the basis for the calculations.

This patient group is limited to the target population via 9 calculation steps:

1. The proportion of lung cancer patients with NSCLC is approx. 80.3–82%.[2]
2. Of these, 49.2% are Stage IV patients.[3]
3. The proportion of activating EGFR mutations is approx. 4.9–10.3%.[2,4]
4. The proportion with ALK translocations is approx. 2–3.9%. [5,]
5. For sub-population a), the sum of the driver mutations from sub-steps 3 and 4 is subtracted from sub-step 2.
6. Non-squamous histology is present in 63.1% of Stage IIIB/IV NSCLC patients. [6]
7. First-line therapy is performed in 76.9 to 78.5% of cases.[3]

8a. The proportion of patients with Stage IV NSCLC with PD-L1 expressing tumours (TPS < 50%) is 71.1%.

8b. The proportion of patients with Stage IV NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) is 28.9%. [3]

9. Number of SHI patients: 85.9%. [7]

For

a) Adults with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations, first-line therapy

approx. 2,320 to 2,640 patients

b) Adults with metastatic non-squamous non-small cell lung cancer; and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression); first-line therapy; or a EGFR mutant or ALK-positive NSCLC independent of the tumour proportion score [TPS] after pre-treatment with an appropriate targeted therapy

approx. 6,670 to 6,950 patients

[2] Resolution on osimertinib of 17 January 2019
[3] Resolution on pembrolizumab of 3 August 2017
[4] Data are based on the proportional values independent of histology (squamous vs non-squamous)
[5] Resolution on crizotinib of 16 June 2016
[6] Resolution on nivolumab of 20 October 2016
[7] Resolution on pembrolizumab of 19 September 2019

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: 11 February 2020):

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

Treatment with atezolizumab may only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and pneumology, specialists in pulmonary medicine, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with non-small cell lung cancer.

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 includes, in particular, instructions on how to deal with the immune mediated side effects potentially occurring under atezolizumab treatment as well as infusion-related 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: 10 January 2020).

According to the product information, the recommended dose of atezolizumab in combination therapy with paclitaxel, carboplatin, and bevacizumab during the induction phase is 1,200 mg every three weeks for four or six cycles. The induction phase is followed by a maintenance phase without chemotherapy; during this phase, Tecentriq (1,200 mg) followed by bevacizumab is administered intravenously every three weeks.

The recommended dosage for pembrolizumab in monotherapy is 200 mg every 3 weeks or 400 mg every 6 weeks. The three-week therapy scheme is used to calculate the costs.

According to the product information (Cisplatin Accord (last revised: July/2017) cisplatin is dosed differently depending on the combination partner. According to the product information of the combination partners, the single dose of cisplatin in combination with vinorelbine or gemcitabine is 75–100 mg/m², in combination with docetaxel or pemetrexed, 75 mg/m², and in combination with paclitaxel, 80 mg/m².

Carboplatin is based on a cycle duration of 3 weeks. For the use of carboplatin in the off-label indication “combination therapy for advanced NSCLC”, the dosage specified in Annex VI of the Pharmaceuticals Directive is up to 500 mg/m² or AUC 6.0 (Area Under the Curve). For the use of carboplatin in combination with nab-paclitaxel, the dosage of AUC 6.0 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”, the time intervals between individual treatments, and for the maximum treatment duration if specified in the product information.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Induction therapy				
Atezolizumab	1 × per 21-day cycle	4–6 cycles	1	4–6
+ carboplatin	1 × per 21-day cycle	4–6 cycles	1	4–6
+ paclitaxel	1 × per 21-day cycle	4–6 cycles	1	4–6
+ bevacizumab	1 × per 21-day cycle	4–6 cycles	1	4–6
Maintenance treatment				
Atezolizumab	1 × per 21-day cycle	11.4–13.4 cycles	1	11.4–13.4
Bevacizumab	1 × per 21-day cycle	11.4–13.4 cycles	1	11.4–13.4
Appropriate comparator therapy				
a) Adults with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line therapy				
Pembrolizumab	1 × per 21-day cycle	17.4 cycles	1	17.4
b) Adults with metastatic non-squamous non-small cell lung cancer; and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression); first-line therapy; or a EGFR mutant or ALK-positive NSCLC independent of the tumour proportion score [TPS] after pre-treatment with an appropriate targeted therapy.				
Cisplatin or carboplatin in combination with a third generation cytostatic agent				
Cisplatin	1 × per 21-day cycle	17.4 cycles	1	17.4
Carboplatin	1 × per 21-day cycle	17.4 cycles	1	17.4
+ docetaxel	1 × per 21-day cycle	17.4 cycles	1	17.4
+ gemcitabine	2 × per 21-day cycle	17.4 cycles	2	34.8
+ paclitaxel	1 × per 21-day cycle	17.4 cycles	1	17.4
+ pemetrexed	1 × 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
+ vinorelbine	2 × per 21-day cycle	17.4 cycles	2	34.8
Carboplatin in combination with nab-paclitaxel				
Carboplatin	1 × per 21-day cycle	17.4 cycles	1	17.4
+ nab-paclitaxel	3 × per 21-day cycle	17.4 cycles	3	52.2

Usage and consumption:

The body surface calculated using the Du Bois formula using an average body weight of 77.0 kg and an average body height of 1.72 m (according to the 2017 microcensus) = 1.90 m² (calculated to 2 decimal places). Differences between women and men were not to be considered because of the therapeutic indication.[8]

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					
Induction therapy					
Atezolizumab	1200 mg	1200 mg	1 × 1200 mg	4–6	4 × 1200 mg – 6 × 1200 mg
+ carboplatin	500 mg/m² = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	4–6	4 × 600 mg + 4 × 450 mg – 6 × 600 mg + 6 × 450 mg
+ paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	1 × 150 mg + 2 × 100 mg	4–6	4 × 150 mg + 8 × 100 mg – 6 × 150 mg + 12 × 100 mg
+ bevacizumab	7.5 mg/kg = 577.5 mg or 15 mg/kg = 1155 mg	577.5 mg or 1155 mg	1 × 400 mg + 2 × 100 mg or 3 × 400 mg	4–6	4 × 400 mg + 8 × 100 mg – 6 × 400 mg + 12 × 100 mg or

[8] https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/koerpermasse-5239003179005.html

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					12 × 400 mg – 18 × 400 mg
Maintenance treatment					
Atezolizumab	1200 mg	1200 mg	1 × 1200 mg	11.4 – 13.4	11.4 × 1200 mg – 13.4 × 1200 mg
Bevacizumab	7.5 mg/kg = 577.5 mg or 15 mg/kg = 1155 mg	577.5 mg or 1155 mg	1 × 400 mg + 2 × 100 mg or 3 × 400 mg	11.4 – 13.4	11.4 × 400 mg + 22.8 × 100 mg – 13.4 × 400 mg + 26.8 × 100 mg or 34.2 × 400 mg – 40.2 × 400 mg
Appropriate comparator therapy					
a) Adults with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line therapy					
Pembrolizumab	200 mg	200 mg	2 × 100 mg	17.4	34.8 × 100 mg
b) Adults with metastatic non-squamous non-small cell lung cancer; and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression); first-line therapy; or a EGFR mutant or ALK-positive NSCLC independent of the tumour proportion score [TPS] after pre-treatment with an appropriate targeted therapy.					
Cisplatin or carboplatin in combination with a third generation cytostatic agent					
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 × 100 mg + 1 × 50 mg	17.4	17.4 × 100 mg + 17.4 × 50 mg
	80 mg/m² = 152 mg	152 mg	1 × 100 mg + 1 × 50 mg + 1 × 10 mg	17.4	17.4 × 100 mg + 17.4 × 50 mg + 17.4 × 10 mg
	100 mg/m² = 190 mg	190 mg	2 × 100 mg	17.4	34.8 × 100 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17.4	17.4 × 600 mg + 17.4 × 450 mg
+ docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 × 160 mg	17.4	17.4 × 160 mg
+ gemcitabine	1250 mg/m² = 2375 mg	2375 mg	1 × 2,000 mg + 2 × 200 mg	34.8	34.8 × 2,000 mg + 69.6 × 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
+ paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	1 × 150 mg + 2 × 100 mg	17.4	17.4 × 150 mg + 34.8 × 100 mg
+ pemetrexed	500 mg/m² = 950 mg	950 mg	2 × 500 mg	17.4	34.8 × 500 mg
+ vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 × 50 mg	34.8	34.8 × 50 mg
	30 mg/m² = 57 mg	57 mg	1 × 50 mg + 1 × 10 mg	34.8	34.8 × 50 mg + 34.8 × 10 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17.4	17.4 × 600 mg + 17.4 × 450 mg
+ nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 × 100 mg	52.2	104.4 × 100 mg

Costs:

Costs of the medicinal product:

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 Sections 130 and 130 a 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.

Designation of the therapy	Package 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					
Induction therapy					
Atezolizumab	1 CIS	€ 4,692.05	€ 1.77	€ 264.69	€ 4,425.59
Carboplatin 450 mg	1 CIS	€ 227.97	€ 1.77	€ 10.29	€ 215.91
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Paclitaxel 100 mg	1 CIS	€ 360.27	€ 1.77	€ 16.57	€ 341.93

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Paclitaxel 150 mg	1 CIS	€ 535.31	€ 1.77	€ 24.88	€ 508.66
Bevacizumab 100 mg	1 CIS	€ 446.21	€ 1.77	€ 24.09	€ 420.35
Bevacizumab 400 mg	1 CIS	€ 1633.01	€ 1.77	€ 89.99	€ 1541.25
Maintenance treatment					
Atezolizumab	1 CIS	€ 4,692.05	€ 1.77	€ 264.69	€ 4,425.59
Bevacizumab 100 mg	1 CIS	€ 474.17	€ 1.77	€ 25.64	€ 446.76
Bevacizumab 400 mg	1 CIS	€ 1,689.86	€ 1.77	€ 93.23	€ 1,594.86
Appropriate comparator therapy					
a) Adults with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line therapy					
Pembrolizumab	1 CIS	€ 3,083.93	€ 1.77	€ 172.85	€ 2,909.31
b) Adults with metastatic non-squamous non-small cell lung cancer; and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression); first-line therapy; or a EGFR mutant or ALK-positive NSCLC independent of the tumour proportion score [TPS] after pre-treatment with an appropriate targeted therapy.					
Cisplatin or carboplatin in combination with a third generation cytostatic agent					
Cisplatin 10 mg	1 CIS	€ 17.26	€ 1.77	€ 0.30	€ 15.19
Cisplatin 50 mg	1 CIS	€ 47.43	€ 1.77	€ 1.73	€ 43.93
Cisplatin 100 mg	1 CIS	€ 76.31	€ 1.77	€ 3.10	€ 71.44
Carboplatin 450 mg	1 CIS	€ 227.97	€ 1.77	€ 10.29	€ 215.91
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Docetaxel	1 CIS	€ 1,397.36	€ 1.77	€ 175.44	€ 1,220.15
Gemcitabine 200 mg	1 CIS	€ 28.57	€ 1.77	€ 0.83	€ 25.97

Designation of the therapy	Package size	Costs (pharmacy sales price)	Re-bate Sec-tion 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory re-bates
Gemcitabine 2000 mg	1 CIS	€ 193.96	€ 1.77	€ 8.68	€ 183.51
Paclitaxel 100 mg	1 CIS	€ 360.27	€ 1.77	€ 16.57	€ 341.93
Paclitaxel 150 mg	1 CIS	€ 535.31	€ 1.77	€ 24.88	€ 508.66
Pemetrexed	1 PIK	€2,533.30	€ 1.77	€ 558.64	€ 1,972.89
Vinorelbine 10 mg	10 CIS	€ 293.74	€ 1.77	€ 13.42	€ 278.55
Vinorelbine 50 mg	10 CIS	€ 1,424.29	€ 1.77	€ 67.07	€ 1,355.45
Carboplatin in combination with nab-paclitaxel					
Carboplatin 450 mg	1 CIS	€ 227.97	€ 1.77	€ 10.29	€ 215.91
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Nab-paclitaxel	1 PIS	€ 429.09	€ 1.77	€ 52.91	€ 374.41

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 March 2020

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 by the statutory health insurance in accordance with Annex I of the Pharmaceuticals Directive (OTC exemption list) are not subject to the current medicinal product price regulation. Instead, in accordance with Section 129, paragraph 5aSGB V) when a non-prescription medicinal product is sold and invoiced in accordance with Section 300, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

Designation of the therapy	Package 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							
Anti-emetic treatment							
In clinical practice, appropriate anti-emetic treatment is established before and/or after cisplatin administration. The product information of cisplatin does not contain any concrete information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% infusion solution, 37.5 g/day	10 × 500 ml IS	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
Sodium chloride 0.9% infusion solution, 3–4.4 l/day	10 × 1,000 ml IS	€ 35.47	€ 1.77	€ 1.12	€ 32.58	17.4	€ 170.07 –
	10 × 500 ml IS	€ 22.72	€ 1.14	€ 0.69	€ 20.89		€ 263.11
Paclitaxel							
Dexamethasone 20 mg[9]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84	17.4	€ 81.32
Dimetindene i.v. 1 mg/10 kg	5 × 4 mg SFI	€ 18.62	€ 1.77	€ 1.97	€ 14.88	17.4	€ 103.56
Ranitidine 50 mg, i.v.	5 CIS	€ 15.08	€ 1.77	€ 0.19	€ 13.12	17.4	€ 45.66
Pemetrexed							
Dexamethasone[7] 2 × 4 mg	100 TAB 4 mg	€ 79.27	€ 1.77	€ 5.40	€ 72.10	52.2	€ 75.27
Folic acid: 350–1,000 µg/day[10]	100 × 400 µg TAB	€ 15.96	€ 0.80	€ 2.34	€ 12.82	365	€ 46.79 – 93.59
Vitamin B12[7] 1,000 µg/day	10 × 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.33	€ 6.70	6	€ 4.02
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; IS: infusion solution; TAB = tablets							

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to

[9] Fixed reimbursement rate

[10] The cost of folic acid is calculated on the basis of the single dose of 400 µg of the non-divisible tablets available for cost calculation, based on a dose range of 400–800 µg per day, even if a dose range of 350–1000 µg is specified in the product information.

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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 10. Supplementary Agreement to the Agreement on Pricing of Substances and Preparations of Substances of 1 March 2020), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 June 2018.

On 24 September 2019, 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 2 VerfO.

By letter dated 26 September 2019 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 27 December 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 January 2020. The deadline for submitting written statements was 23 January 2020.

The oral hearing was held on 10 February 2020.

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 were discussed at the session of the subcommittee on 24 March 2020, and the proposed resolution was approved.

On 2 April 2020, the G-BA resolved by written statement to amend the Pharmaceuticals Directive.

The patient representatives support the resolution.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	26 June 2018	Determination of the appropriate comparator therapy
Working group Section 35a	5 February 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	10 February 2020	Conduct of the oral hearing
Working group Section 35a	19 February 2020 4 March 2020 17 March 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	24 March 2020	Concluding discussion of the draft resolution
Plenum	2 April 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 April 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken