Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Atezolizumab (new therapeutic indication: non-small cell lung cancer, first-line)

of 20 March 2025

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 all reimbursable medicinal products with new active ingredients. For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

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

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

2. Key points of the resolution

The active ingredient 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 26 August 2024, 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 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 20 September 2024, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 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 advanced NSCLC who are ineligible for platinum-based therapy".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 January 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of 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 advanced NSCLC who are ineligible for platinum-based therapy.

Therapeutic indication of the resolution (resolution of 20 March 2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with advanced NSCLC with PD-L1 expression ≥ 50% on TC considered ineligible for platinum; first-line therapy

Appropriate comparator therapy for atezolizumab as monotherapy:

− Pembrolizumab as monotherapy

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

or

− cemiplimab as monotherapy

b) Adults with locally advanced NSCLC with PD-L1 expression < 50% on TC considered ineligible for platinum; first-line therapy

Appropriate comparator therapy for atezolizumab as monotherapy:

− Gemcitabine as monotherapy

or

− vinorelbine as monotherapy

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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

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

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

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or

3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

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

On 1. In addition to atezolizumab, the active ingredients cemiplimab, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, pembrolizumab, vindesine and vinorelbine are available in this therapeutic indication in terms of the authorisation status. The marketing authorisations are partly based on the use as monotherapy or in certain combination therapies.

Active ingredients approved for a molecularly stratified therapy (directed against ALK, BRAF, EGFR, -Exon-20, KRAS G12C, METex14 or ROS1) are not considered.

On 2. Non-medicinal treatment is not considered.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:
- Atezolizumab (resolution of 19.11.2021)
- Cemiplimab (resolution of 20.01.2022)
- Pembrolizumab (resolution of 03.08.2017)

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V.

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

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

Moreover, it is assumed that no molecularly stratified therapy (directed against ALK, BRAF, EGFR, -Exon-20, KRAS G12C, METex14 or ROS1) will be considered for patients at the time of therapy with atezolizumab. Based on the available evidence on therapy options depending on PD-L1 expression, the appropriate comparator therapy is differentiated into two sub-populations with a cut-off value of PD-L1 expression of 50% of tumour cells:

a) Adults with advanced NSCLC with PD-L1 expression ≥ 50% of TC considered ineligible for platinum; first-line therapy

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

The combination therapies of ICI and platinum-based chemotherapy also recommended in the guidelines cannot be considered due to the lack of suitability of the patients for platinum-based therapy in this therapeutic indication.

Since atezolizumab is the medicinal product to be assessed, a comparison with atezolizumab with regard to the research question of the benefit assessment according to Section 35a SGB V is not possible.

In the benefit assessment of pembrolizumab for the first-line treatment of metastatic NSCLC with PD-L1 expression ≥ 50% of TC, there was an indication of a considerable additional benefit compared to platinum-based chemotherapy (resolution of 3 August 2017). In the benefit assessment of cemiplimab, no additional benefit over pembrolizumab could be determined due to the absence of suitable data (resolution of 20 January 2022).

In the written opinion of the scientific-medical societies on the question of comparator therapy for the present indication, therapy with atezolizumab, cemiplimab or pembrolizumab is seen as a treatment standard.

In the overall assessment, monotherapies with pembrolizumab or cemiplimab were determined to be equally appropriate comparator therapies.

b) Adults with locally advanced NSCLC with PD-L1 expression < 50% of TC considered ineligible for platinum; first-line therapy

For first-line treatment of patients with metastatic NSCLC with PD-L1 expression in < 50% of TC who cannot receive platinum-based combination chemotherapy, the guidelines recommend monotherapy with a third-generation cytostatic, regardless of the tumour histology.

Furthermore, the ICI atezolizumab is available as monotherapy, which, in contrast to the other ICIs, is also indicated in monotherapy with a PD-L1 expression of < 50%. Specifically, atezolizumab is approved as monotherapy from a PD-L1 expression ≥ 10% in tumour-infiltrating immune cells. Since atezolizumab is the medicinal product to be assessed, a comparison with atezolizumab with regard to the research question of the benefit assessment according to Section 35a SGB V is not possible.

In the written opinion of the scientific-medical societies on the question of comparator therapy for the present indication, a monochemotherapy with gemcitabine or vinorelbine is seen as a treatment standard.

As a result, the monotherapies with gemcitabine or vinorelbine were determined to be equally appropriate comparator therapies.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

a) Adults with advanced NSCLC with PD-L1 expression ≥ 50% on TC considered ineligible for platinum; first-line therapy

An additional benefit is not proven.

Justification:

No data are available to allow an assessment of the additional benefit. In their dossier, the pharmaceutical company does not consider patient population a) and accordingly does not present any data for the assessment of the additional benefit.

b) Adults with locally advanced NSCLC with PD-L1 expression < 50% of TC considered ineligible for platinum; first-line therapy

Indication of a minor additional benefit

Justification:

For the benefit assessment on patient population b), the pharmaceutical company presented results from the completed, open-label, randomised, controlled phase III IPSOS study. The study was conducted in 83 study sites in Asia, Europe, North and South America between September 2017 and October 2023.

Adult patients with histologically or cytologically confirmed advanced, relapsed or metastatic stage IIIB, IIIC and IV NSCLC whose tumours had no EGFR mutation or ALK translocations, who were ineligible for platinum-based chemotherapy and who had not received previous systemic therapies were enrolled in the study.

For the present benefit assessment, the pharmaceutical company considered the sub-population of patients with PD-L1 expression < 50% of the tumour cells from the patient population subsequently formed for the marketing authorisation. 229 patients were in the atezolizumab arm and 115 patients were in the gemcitabine or vinorelbine arm.

The primary endpoint of the IPSOS study was overall survival. Other endpoints were assessed in the categories of morbidity, health-related quality of life and side effects.

Two data cut-offs are available for the IPSOS study:

- 15 May 2020 (pre-specified interim analysis of overall survival after 304 events)
- 30 April 2022 (pre-specified final analysis of overall survival after 379 events in the entire study population)

Furthermore, the pharmaceutical company submitted a further evaluation of the data at the time of the last patient's last visit on 26 October 2023 in the written statement procedure. The pharmaceutical company stated that this evaluation mainly contains updates for 15 patients in the intervention arm who continued to be treated with atezolizumab until the end

of the study, both for the endpoint of overall survival and for the endpoints of adverse events. This data update is not used for the benefit assessment as it was not pre-specified.

For the benefit assessment in patient population b), the sub-population (patients with PD-L1 expression < 50% of tumour cells and patients with unknown PD-L1 expression status) of the pre-specified final data cut-off of 30 April 2022 was used.

On the dosage in the comparator arm

The majority of patients in the comparator arm of the study were treated off-label with gemcitabine or vinorelbine (dose level and dosing frequency). However, it is assumed on the basis of the information presented in the written statement procedure that the patients in the comparator arm of the study were essentially treated appropriately. In particular, it is assumed that weekly administration of vinorelbine or gemcitabine without a break in the last week of the cycle is generally not an option for the relevant patient population. Therefore, the IPSOS study is used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall survival in the IPSOS study was operationalised as the time from randomisation to death from any cause.
For the endpoint of overall survival, there was a statistically significant difference to the advantage of atezolizumab compated to gemcitabine or vinorelbine, the extent of which was assessed as a relevant improvement, but no more than a minor improvement.

Morbidity

Progression-free survival (PFS)

Progression-free survival was operationalised in the IPSOS study as the time between randomisation and the time of first disease progression or until death from any cause, depending on the event that occurs first. The endpoint was assessed by the principal investigators using the RECIST criteria version 1.1.

For the PFS endpoint, there was no statistically significant difference between the treatment groups.

The present PFS endpoint is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is collected according to RECIST criteria and thus predominantly by means of imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology (EORTC QLQ-C30 and EORTC QLQ-LC13)
The symptomatology of the patients is assessed in the IPSOS study with the EORTC QLQ-C30 and the disease-specific additional module EORTC QLQ-LC13.
Due to the strongly decreasing and differential return rates as well as different data collection time points of the patient-reported endpoints within the treatment cycles, the results on the patient-reported endpoints cannot be interpreted meaningfully and are therefore unsuitable for the benefit assessment.

Health status (EQ-5D VAS)
The health status of the patients is assessed in the IPSOS study using EQ-5D VAS.
Due to the strongly decreasing and differential return rates as well as different data collection time points of the patient-reported endpoints within the treatment cycles, the results on the patient-reported endpoints cannot be interpreted meaningfully and are therefore unsuitable for the benefit assessment.

Quality of life

Health-related quality of life (EORTC QLQ-C30)
Patients' quality of life is assessed in the IPSOS study using the EORTC QLQ-C30.
Due to the strongly decreasing and differential return rates as well as different data collection time points of the patient-reported endpoints within the treatment cycles, the results on the patient-reported endpoints cannot be interpreted meaningfully and are therefore unsuitable for the benefit assessment.

Side effects

Adverse events (AEs)

In the IPSOS study, an adverse event occurred in 93% of patients in the intervention arm and 98.2% thereof in the comparator arm. The results were only presented additionally.

SAEs
For the endpoint of SAEs, no statistically significant difference was detected between the treatment groups.

Severe AEs
For the endpoint of severe AEs, there was a statistically significant difference to the advantage of atezolizumab compared to gemcitabine or vinorelbine.

Therapy discontinuation due to AEs
For the endpoint of discontinuation due to AEs, no statistically significant difference was detected between the treatment groups. However, there was an effect modification due to the sex characteristic. For men, there was a statistically significant difference to the advantage of atezolizumab compared to the appropriate comparator therapy. For women, there was no statistically significant difference between the treatment groups. In view of the fact that this effect modification is only shown for this single endpoint, the result for the total population is used for the assessment.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs
The pharmaceutical company does not provide a summary analysis of immune-mediated events for immune-mediated AEs (SAEs and severe AEs). Instead, they present results for individual AESI categories in Module 4 A as part of the analyses of AEs of special interest (AESI), each of which only depicts a sub-area of immune-mediated AEs. The analyses submitted by the pharmaceutical company are unsuitable for comprehensively depicting immune-mediated AEs. Thus, no suitable data are available for immune-mediated AEs (SAEs and severe AEs).

Neutropenia
For the endpoint of neutropenia (severe AEs), there was a statistically significant difference to the advantage of atezolizumab compared to gemcitabine or vinorelbine.

Skin reactions
For the endpoint of skin reactions (AEs), there was no statistically significant difference between the treatment groups.

Other specific AEs

Gastrointestinal disorders
For the endpoint of gastrointestinal disorders (AEs), there was a statistically significant difference to the advantage of atezolizumab compared to gemcitabine or vinorelbine.

Overall assessment

For the benefit assessment of atezolizumab as monotherapy for the first-line treatment of adults with advanced NSCLC with PD-L1 expression < 50% who are ineligible for platinum-based therapy, results of the IPSOS study are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects compared to monotherapy with gemcitabine or vinorelbine.
For the endpoint of overall survival, there was a statistically significant difference to the advantage of atezolizumab compated to gemcitabine or vinorelbine, the extent of which was assessed as a relevant improvement, but no more than a minor improvement.
The data on symptomatology (collected using EORTC QLQ-C30 and EORTC QLQ-LC13), health status (collected using EQ-5D VAS) and health-related quality of life (collected using EORTC QLQ-C30) cannot be meaningfully interpreted due to strongly decreasing and differential return rates as well as different data collection time points within the treatment cycles and are therefore unsuitable for the benefit assessment.
In the endpoint category of side effects, there was no statistically significant difference between the study arms concerning the endpoint of serious AEs. For the endpoint of severe AEs (CTCAE grade ≥ 3), there was a statistically significant difference to the advantage of atezolizumab. In addition, there were positive effects of atezolizumab compared to monotherapy with gemcitabine or vinorelbine in detail for some specific AEs. No suitable data were available on immune-mediated SAEs and immune-mediated severe AEs.

In the overall assessment, a minor additional benefit of atezolizumab compared to monotherapy with gemcitabine or vinorelbine was identified.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open-label, randomised, controlled phase III IPSOS study.
The risk of bias for the results of overall survival is classified as low.
No suitable data are available for the endpoints on symptomatology, health status and health-related quality of life. Assessment of symptomatology and health-related quality of life is therefore not possible.
The risk of bias for the results of the endpoints of SAEs, severe AEs is assessed as low.
In addition, the risk of bias is classified as high for the endpoints of non-serious/ non-severe AEs and for the endpoint of therapy discontinuation due to AEs due to the lack of blinding in subjective endpoint assessment.

Overall, an indication is derived for the reliability of data of the additional benefit identified.

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 as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy.

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

a) Adults with advanced NSCLC with PD-L1 expression ≥ 50% on TC considered ineligible for platinum; first-line therapy

and

b) Adults with locally advanced NSCLC with PD-L1 expression < 50% on TC considered ineligible for platinum; first-line therapy

Patient population a)

Monotherapy with pembrolizumab or cemiplimab was determined as the appropriate comparator therapy.

For patient population a), the pharmaceutical company did not submit any data to prove the additional benefit. Therefore, an additional benefit is not proven.

Patient population b)

Monotherapy with gemcitabine or vinorelbine was determined as the appropriate comparator therapy.

For the benefit assessment on patient population b), the pharmaceutical company presented results from the completed, open-label, randomised, controlled phase III IPSOS study.
For the endpoint of overall survival, there was a statistically significant difference to the advantage of atezolizumab compated to gemcitabine or vinorelbine, the extent of which was assessed as a relevant improvement, but no more than a minor improvement.
The data on symptomatology (collected using EORTC QLQ-C30 and EORTC QLQ-LC13), health status (collected using EQ-5D VAS) and health-related quality of life (collected using EORTC QLQ-C30) cannot be meaningfully interpreted due to strongly decreasing and differential return rates as well as different data collection time points within the treatment cycles and are therefore unsuitable for the benefit assessment.
In the endpoint category of side effects, there was no statistically significant difference between the study arms concerning the endpoint of serious AEs. For the endpoint of severe AEs (CTCAE grade ≥ 3), there was a statistically significant difference to the advantage of atezolizumab. In addition, there were positive effects of atezolizumab compared to monotherapy with gemcitabine or vinorelbine in detail for some specific AEs. No suitable data were available on immune-mediated SAEs and immune-mediated severe AEs.

In the overall assessment, a minor additional benefit of atezolizumab compared to gemcitabine or vinorelbine was identified.

The reliability of data of the additional benefit identified is classified in the "indication" category.

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

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

For the number of German patients with lung cancer, the incidence for 2020 (56,690 patients)[2] is used as the basis for the calculations. The current publications lack projected data. This is why later developments cannot be presented here.

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

1. The percentage of lung cancer patients with NSCLC is between 73.6% and 83.6%[3] (41,723 to 47,392 patients).
2. Of these, 46.63% of patients are in stage IV at initial diagnosis[4]. Of the remaining 53.37% of patients who are in stage I-IIIB, 37.7% will progress to stage IV in 2022[5]. The percentage of patients in stage IIIB/IIIC is 4.5% to 6.1%[6]. The total number of patients is 32,273 to 36,658.
3. First-line therapy is given in 76.9% to 96.1%[3] of cases (24,818 - 35,228 patients).
4. Deduction of the percentages of patients with EGFR mutation (10.3% to 14.1%, 1,129 to 3,513 patients)[7] and ALK mutations (2% to 3.9%, 496 to 1,373 patients)[8] (21,765 to 28,887 patients)
5. 10-30% of patients are ineligible for platinum-containing therapy (2,176 to 8,666 patients).
6. In 28.9%[9] of patients, PD-L1 expression ≥ 50% of TC (629 to 2,504 patients) (PD-L1 expression < 50% of TC in 1,547 to 6,161 patients)
7. Taking into account 87.28% of SHI-insured patients, there are 549 to 2,185 patients in first-line therapy for tumours with PD-L1 expression ≥ 50% of TC and 1,350 to 5,377 patients for tumours with PD-L1 expression < 50% of TC.

[2] Robert Koch Institute, Society of Epidemiological Cancer Registries in Germany. Cancer in Germany for 2019/2020. 2023

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

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

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

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

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

[8] Benefit assessment according to Section 35a SGB V, A22-31, lorlatinib, 30.05.2022

[9] Benefit assessment according to Section 35a SGB V, A21-98, cemiplimab, 25.10.2021

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 2025):

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

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

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

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

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2025).

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

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916).[10]

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

Treatment period:

a) Adults with locally advanced or metastatic NSCLC with PD-L1 expression ≥ 50% of TC who are considered ineligible for platinum and whose disease does not have an EGFR mutation or ALK translocation; first-line therapy

[10] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

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 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Pembrolizumab as monotherapy				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Cemiplimab as monotherapy				
Cemiplimab	1 x per 21-day cycle	17.4	1	17.4

b) Adults with locally advanced or metastatic NSCLC with PD-L1 expression ≥ 50% of TC who are considered ineligible for platinum and whose disease does not have an EGFR mutation or ALK translocation; first-line therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Atezolizumab	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Monotherapy with gemcitabine				
Gemcitabine	3 x per 28-day cycle	13.0	3	39.0
Monotherapy with vinorelbine				
Vinorelbine	1 x every 7 days	52.1	1	52.1

Consumption:

a) Adults with locally advanced or metastatic NSCLC with PD-L1 expression ≥ 50% of TC who are considered ineligible for platinum and whose disease does not have an EGFR mutation or ALK translocation; first-line therapy

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	17.4	17.4 x 1,875 mg
Appropriate comparator therapy					
Pembrolizumab as monotherapy					
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
Cemiplimab as monotherapy					
Cemiplimab	350 mg	350 mg	1 x 350 mg	17.4	17.4 x 350 mg

b) Adults with locally advanced or metastatic NSCLC with PD-L1 expression ≥ 50% of TC who are considered ineligible for platinum and whose disease does not have an EGFR mutation or ALK translocation; first-line therapy

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	17.4	17.4 x 1,875 mg
Appropriate comparator therapy					
Monotherapy with gemcitabine					
Gemcitabine	1,000 mg/m^2 BSA = 1,910 mg	1,910 mg	2 x 1,000 mg	39.0	78 x 1,000 mg
Monotherapy with vinorelbine					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Vinorelbine	25 mg/m² BSA = 47.8 mg - 30 mg/m² BSA = 57.3 mg	47.8 mg - 57.3 mg	1 x 50 mg - 1 x 50 mg + 1 x 10 mg	52.1	52.1 x 50 mg - 52.1 x 50 mg + 52.1 x 10 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Atezolizumab 1,875 mg	1 SFI	€ 4,129.23	€ 1.77	€ 232.53	€ 3,894.93
Appropriate comparator therapy					
Cemiplimab 350 mg	1 CIS	€ 4,326.55	€ 1.77	€ 243.80	€ 4,080.98
Gemcitabine 1,000 mg	1 PIS	€ 102.35	€ 1.77	€ 10.62	€ 89.96
Pembrolizumab 100 mg	1 CIS	€ 2,743.07	€ 1.77	€ 153.37	€ 2,587.93
Vinorelbine 50 mg	1 CIS	€ 152.64	€ 1.77	€ 6.71	€ 144.16
Vinorelbine 10 mg	1 CIS	€ 38.90	€ 1.77	€ 1.31	€ 35.82
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIS = powder for the preparation of an infusion solution					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services need to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 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 agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve

antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from

a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the

combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adults with advanced NSCLC with PD-L1 expression ≥ 50% on TC considered ineligible for platinum; first-line therapy

   No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b) Adults with locally advanced NSCLC with PD-L1 expression < 50% on TC considered ineligible for platinum; first-line therapy

   No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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 their session on 7 February 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. Working group 35a newly determined the appropriate comparator therapy at their session on 3 September 2024.

On 23 September 2024, 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 23 September 2024, 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 19 December 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2025. The deadline for submitting statements was 23 January 2025.

The oral hearing was held on 10 February 2025.

By letter dated 11 February 2025, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on DD. MM YYYY.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 11 March 2025, and the proposed draft resolution was approved.

At its session on 20 March 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	7 February 2023	Determination of the appropriate comparator therapy
Working group Section 35a	3 September 2024	New determination of the appropriate comparator therapy
Working group Section 35a	4 February 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 February 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 February 2025 4 March 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 March 2025	Concluding discussion of the draft resolution
Plenum	20 March 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 March 2025

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

Prof. Hecken