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, PD-L1 expression ≥ 50%, adjuvant therapy after resection and chemotherapy)

of 5 January 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

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

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

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

2. Key points of the resolution

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

On 7 June 2022, Tecentriq 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, p. 7).

On 4 July 2022, 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 of the 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 (non-small cell

lung cancer, PD-L1 expression ≥ 50% of TC, EGFR/ALK negative, adjuvant treatment following resection and chemotherapy).

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 17 October 2022, 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 Methods1 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 as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1 for selection criteria).

Therapeutic indication of the resolution (resolution of 05.01.2023):

see the approved therapeutic indication

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with completely resected NSCLC with a high risk of recurrence after platinum-based chemotherapy whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC

Appropriate comparator therapy for atezolizumab as monotherapy:

Monitoring wait-and-see approach

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

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the 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.

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

On 1. Based on the authorisation status, the active ingredient vinorelbine is available in the therapeutic indication.

On 2. For patients with completely resected NSCLC, adjuvant cisplatin-based chemotherapy may be followed by radiotherapy in individual cases. However, this is not applied on a regular basis.

On 3. For the planned therapeutic indication, there are no resolutions or guidelines of the G-BA for medicinal applications or non-medicinal treatments.

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

The guidelines do not recommend any other medicinal or non-medicinal adjuvant treatment for patients with completely resected NSCLC after adjuvant cisplatin-based chemotherapy (and in individual cases, but not regularly, subsequent radiotherapy). Since patients in the therapeutic indication are considered disease-free, the recommendations of the guidelines are limited to after-care with the aim of early diagnosis of recurrences.

In view of the present treatment setting and taking into account the available evidence and the recommendations on after-care, the G-BA determined "monitoring wait-and-see approach" as an appropriate comparator therapy.

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:

Hint for a non-quantifiable additional benefit

Justification:

For the benefit assessment, the pharmaceutical company presents results from the multicentre, open-label randomised IMpower010 study, comparing atezolizumab with best supportive care (BSC). The BSC comparison carried out in the IMpower010 study corresponds to an implementation of the appropriate comparator therapy consisting of the monitoring wait-and-see approach.

The ongoing study started in October 2015 is being conducted in 204 study sites across Europe, North America, Asia and Australia.

Adult patients with histologically or cytologically confirmed stage IB - IIIA NSCLC (UICC/AJCC classification according to the 7th edition) following complete tumour resection were enrolled in the study, regardless of PD-L1 expression and EGFR and ALK mutational status. The patients had to have also a good general condition, with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1. In addition, patients had to be eligible for cisplatin-containing combination chemotherapy.

The study is divided into a recruitment phase and a subsequent randomisation phase. In the recruitment phase, patients (N = 1280) received adjuvant cisplatin-based combination chemotherapy of investigator's choice (cisplatin in combination with vinorelbine, docetaxel, gemcitabine, or pemetrexed) for up to 4 cycles.

A total of 1005 patients were enrolled in the randomisation phase of the study and divided in a 1:1 ratio to either treatment with atezolizumab (N = 507) or BSC (N = 498). Randomisation was stratified by sex (male vs female), histology (squamous vs non-squamous), disease stage (IB vs II vs IIIA), and PD-L1 expression in tumour tissue (tumour cells 2/3 and any immune cells vs tumour cells 0/1 and immune cells 2/3 vs tumour cells 0/1 and immune cells 0/1).

In the dossier for the benefit assessment, the pharmaceutical company presents evaluations for the sub-population of patients in stage II to IIIA whose tumours have PD-L1 expression on ≥ 50% of the tumour cells and no mutations in the EGFR or ALK gene or have an unknown mutational status of these genes. As part of the statement, the pharmaceutical company presents data on EGFR and ALK mutational status, which clarify that approximately 90% of patients with unknown mutational status had a squamous cell tumour histology, so that a negative mutational status can be assumed in almost all of these patients even without explicit testing. A further uncertainty, which was noted by IQWiG in the dossier assessment with

regard to the time interval of more than 60 days between tumour resection and adjuvant chemotherapy, was resolved in the course of the written statement procedure by subgroup evaluations for patients with ≤ 60 or > 60 days between tumour resection and adjuvant chemotherapy. Overall, the sub-population includes 106 patients in the atezolizumab arm and 103 patients in the comparator arm.

The treatment with atezolizumab in the intervention arm was carried out according to the specifications in the product information. Switching of patients from the comparator arm to treatment with atezolizumab was not planned in the IMpower010 study.

The primary endpoint of the IMpower010 study is disease-free survival (DFS). Other secondary endpoints include endpoints in the categories of mortality, morbidity, and side effects.

For the ongoing IMpower010 study, 2 data cut-offs are currently available:

- 21.01.2021 (interim analysis of DFS after 193 events (planned after about 190 events))
- 18.04.2022 (interim analysis of overall survival after 251 events (planned after approximately 254 events))

For all endpoints, the pharmaceutical company uses the 2nd data cut-off for benefit assessment. For the DFS, the pharmaceutical company uses the 1st data cut-off.

Limitations of the IMpower010 study

In the IMpower010 study, cerebral metastasis was ruled out by either magnetic resonance imaging (MRI) or computed tomography (CT) scan. However, according to guidelines, only MRI is the procedure of choice for the detection of brain metastases, so there is uncertainty as to whether patients with brain metastases were enrolled in the study.

In addition, the enrolment of patients in the IMpower010 study was based on the 7th edition of the TNM classification according to UICC/AJCC. Based on the information provided by the pharmaceutical company in the dossier, some of the patients are no longer assigned to stages II to IIIA according to the new staging of the 8th edition of the TNM classification according to UICC/AJCC.

Overall, there is uncertainty as to whether all enrolled patients have an indication for adjuvant chemotherapy according to guideline recommendations.

Extent and probability of the additional benefit

Mortality

Overall survival

The overall survival was operationalised in the IMpower10 study as the time from randomisation to death from any cause.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of atezolizumab versus the monitoring wait-and-see approach.

For the assessment of the data on overall survival, it must be taken into account that the information provided by the pharmaceutical company does not clarify for both the 1st and 2nd data cut-offs why no systemic subsequent therapy was carried out in some of the patients with relapse or why no treatment with an immune checkpoint inhibitor was carried out.

With its statement, the pharmaceutical company submits data on performed surgeries and radiotherapies in the patients with relapse. It states that, especially in locoregional recurrences, surgery or radiation alone may represent adequate subsequent therapy. However, the data show that in the comparator arm, surgery and radiotherapy were largely performed for the treatment of remote metastases (correspondingly, the patients were in stage IV, regularly palliative treatment setting) and not for locoregional recurrences. Although it is possible (as also described by the pharmaceutical company) that even in patients with individual remote metastases, local treatment of the metastases by means of surgery or radiotherapy is initially indicated, it can be assumed that in the further progressive course of the disease, also taking into account the therapy standard at the time of the study, there will be an indication for systemic subsequent therapy - with guideline-compliant use of checkpoint inhibitors in the first line - after a certain point of time. Therefore, it should still be criticised that in the comparator arm more than 40% of patients with recurrence did not receive any systemic subsequent therapy at all and more than 50% of patients did not receive any treatment with a checkpoint inhibitor and that this also does not change significantly in the 2nd. data cut-off. Thus, the results in the overall survival endpoint are not quantifiable, even taking into account the data from the written statement procedure.

Morbidity

Disease-free survival (DFS) and recurrence rate

Disease-free survival (DFS) in the IMpower010 study is defined as the time from randomisation to the first occurrence of any of the following events, whichever occurred first: first documented recurrence of disease, occurrence of new primary NSCLC, death from any cause.

The patients in the present therapeutic indication are treated with a curative therapeutic approach: adjuvant therapy after complete resection of the primary tumours and possibly affected lymph nodes. The remaining tumour cells can cause a recurrence in the further course. Recurrence means that the attempt at a cure by the curative therapeutic approach was unsuccessful. The occurrence of a recurrence is patient-relevant.

The combined endpoint in the IMpower010 study includes the following individual components:

- Local recurrence
- Regional recurrence
- Remote recurrence
- CNS metastasis
- New primary NSCLC
- Death without recurrence

The pharmaceutical company shall submit evaluations exclusively for the 1st data cut-off from January 2021. These cover only about 70% of the observation period of the IMpower010 study. Although due to the longer duration of observation for the 2nd data cut-off, data with a higher information content are available, they are not submitted by the pharmaceutical

company in the dossier as well as in the written statement procedure. The pharmaceutical company argues that two pre-specified analyses of DFS are performed: Interim analysis in January 2021 and final analysis expected in late 2023. From the pharmaceutical company's point of view, in order to comply with international standards and guidelines on Good Clinical Practice, it would not be necessary to evaluate the DFS for the 2nd data cut-off. In addition, it states that the interim analysis already forms the basis for the European marketing authorisation and is therefore sufficient from the pharmaceutical company's point of view.

This approach of the pharmaceutical company is not followed. In principle, according to the dossier template, corresponding evaluations for all patient-relevant endpoints are to be submitted for the submitted data cut-offs, even if a data cut-off was originally planned only for the evaluation of individual endpoints. Therefore, the criticism of the pharmaceutical company's approach remains valid even after the conclusion of the written statement procedure and it is stated that the evaluations on morbidity from the IMpower010 study submitted by the pharmaceutical company are not usable for the benefit assessment.

Quality of life

Data on health-related quality of life were not collected in the IMpower010 study.

Side effects

The pharmaceutical company submits results on all adverse events (AEs) according to SOC and PT in the dossier without considering the frequency thresholds according to the dossier template. Evaluations using the thresholds of the dossier template will be provided as part of the written statement procedure. In addition, the evaluation of immune-mediated AEs (AEs, serious UE, severe AEs) presented in the dossier is not suitable to comprehensively illustrate immune-mediated AEs.

Adverse events (AEs) in total

In the IMpower010 study, AEs occurred in both study arms in majority of the patients enrolled. The results were only presented additionally.

Serious AEs (SAEs)

For the endpoint of SAE, there is a statistically significant disadvantage of atezolizumab versus the monitoring wait-and-see approach.

Severe AEs (CTCAE grade ≥ 3)

There is no statistically significant difference between the treatment arms for the endpoint of severe AEs (CTCAE grade ≥ 3).

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, there is a statistically significant disadvantage of atezolizumab versus the monitoring wait-and-see approach.

Specific AEs

Immune-mediated SAEs and immune-mediated severe AEs

No usable data are available for the endpoints of immune-mediated SAEs and immune-mediated severe AEs.

Other specific AEs

For the endpoints of fever (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), and infections and infestations (SOC, SAEs), atezolizumab shows a statistically significant disadvantage compared with the monitoring wait-and-see approach.

In summary, a disadvantage of atezolizumab treatment can be identified due to several negative effects in SAEs and discontinuations due to AEs, and in detail, specific AEs.

Overall assessment

The benefit assessment of atezolizumab as monotherapy for adjuvant treatment of NSCLC following complete resection and platinum-based chemotherapy in adult patients at high risk for recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells and do not have EGFR-mutated or ALK-positive NSCLC is based on results of the IMpower010 study on the endpoint categories of mortality, morbidity, and side effects compared with the monitoring wait-and-see approach. The pharmaceutical company submits evaluations for the sub-population of stage II to IIIA patients whose tumours have PD-L1 expression on ≥ 50% of tumour cells and no mutations in the EGFR or ALK genes or have an unknown mutational status of these genes.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of atezolizumab compared to the monitoring wait-and-see approach. When interpreting the result, it should be taken into account that a relevant percentage of patients with relapse in the comparator arm of the IMpower010 study may be assumed to have received inadequate subsequent therapy with respect to the therapy standard during the study period. Overall, therefore, relevant uncertainties remain regarding the assessment of the magnitude of the statistically significant difference to the advantage of atezolizumab versus the monitoring wait-and-see approach in terms of transferability to the reality of care.

There are no usable results for the patient-relevant endpoints of DFS and recurrences in the morbidity category. The avoidance of recurrences is a significant therapeutic goal in view of the present curative therapeutic goal.

Endpoints on health-related quality of life were not assessed in the IMpower010 study.

For the side effects, there is no statistically significant difference between the study arms concerning the endpoint of severe AEs (CTCAE grade ≥ 3). For the endpoints of serious AEs and discontinuation due to AEs, and in detail for specific AEs, there are negative effects of atezolizumab compared to the monitoring wait-and-see approach.

In the overall analysis, the positive effect on overall survival is offset by relevant disadvantages in terms of side effects. These disadvantages are weighted against the background of the present curative therapeutic approach and do not question the entire positive effect on overall survival. The magnitude of the effect on overall survival indicates a clinically significant improvement compared with the monitoring wait-and-see approach, but this cannot be quantified with certainty against the background of the uncertainties described.

Therefore, in the overall assessment, atezolizumab as monotherapy for adjuvant treatment of NSCLC following complete resection and platinum-based chemotherapy in adult patients at

high risk for recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and do not have EGFR-mutated or ALK-positive NSCLC is found to have a non-quantifiable additional benefit over the monitoring wait-and-see approach.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, open-label, phase III IMpower010 study.

The cross-endpoint risk of bias of the IMpower010 study is estimated to be low.

For SAEs and severe AEs, the risk of bias is considered low.

For discontinuation due to AEs, the open-label study design results in a high risk of bias.

Overall, there are uncertainties as to whether all patients enrolled have an indication for adjuvant chemotherapy according to the guideline recommendation, since both the detection of brain metastases for a percentage of patients was not in accordance with the guideline and a percentage of patients can no longer be assigned to stages II to IIIA according to the new staging of the 8th edition of the TNM classification according to UICC/AJCC.

In addition, the reliability of data of the overall assessment of the additional benefit is limited by the fact that no usable data can be used for the endpoints of DFS and recurrences of the endpoint category of morbidity and that no data on health-related quality of life have been collected.

Overall, a hint is derived for the reliability of data of the additional benefit identified.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of atezolizumab finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The present results on overall survival and side effects are based on the 2nd data cut-off from 18 April 2022 of the IMpower010 study. The data on disease-free survival at the time of the 2nd data cut-off are not available. Thus, the significance is limited and uncertainties remain. The pre-specified final analysis of disease-free survival was announced by the pharmaceutical company during the written statement procedure for Q3 2023.

Since more clinical data are expected which are relevant for the benefit assessment of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of atezolizumab. The limitation enables other results from the IMpower010 study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V.

For this purpose, a limitation of the resolution until 1 April 2024 to be appropriate.

Conditions of the limitation:

For the new benefit assessment after expiry of the deadline, the IMpower010 study results on all patient-relevant endpoints used for the evidence of an additional benefit are to be presented in the dossier.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment of the medicinal product atezolizumab recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of atezolizumab in relation to the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product atezolizumab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1, paragraph 2, nos. 2 to 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

This assessment is a benefit assessment of a new therapeutic indication for the active ingredient atezolizumab as monotherapy: adjuvant treatment of NSCLC following complete resection and platinum-based chemotherapy in adult patients at high risk of recurrence whose tumours have PD-L1 expression at ≥ 50% and do not have EGFR-mutated or ALK-positive NSCLC.

The appropriate comparator therapy is determined as follows:

monitoring wait-and-see approach.

For the assessment of the additional benefit of atezolizumab, results from the randomised, open-label IMpower010 study were presented on the endpoint categories of mortality, morbidity, and side effects compared with the monitoring wait-and-see approach.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of atezolizumab compared to the monitoring wait-and-see approach. Relevant uncertainties remain regarding the assessment of the extent in terms of transferability to the reality of care.

Considering the present curative therapeutic approach, the avoidance of recurrences represents a significant therapeutic goal. However, the results presented for the endpoints of disease-free survival (DFS) and recurrence rate are not usable. The background is that no data on these endpoints were submitted by the pharmaceutical company for the 2nd data cut-off, although this data cut-off has a higher information content due to the longer duration of observation.

Endpoints on health-related quality of life were not collected.

Negative effects of atezolizumab are present for the endpoints of serious AEs and discontinuation due to AEs, and in detail for specific AEs.

In the overall analysis, the positive effect on overall survival is offset by relevant disadvantages in terms of side effects. These disadvantages do not call into question the entire positive effect on overall survival. The magnitude of the effect on overall survival indicates a clinically significant improvement compared with the monitoring wait-and-see approach, but this cannot be quantified with certainty against the background of the uncertainties described.

Overall, therefore, a non-quantifiable additional benefit is established for atezolizumab as monotherapy for adjuvant treatment of NSCLC following complete resection and platinum-based chemotherapy in adult patients at high risk of recurrence whose tumours have PD-L1 expression at ≥ 50% and do not have EGFR-mutated or ALK-positive NSCLC versus the monitoring wait-and-see approach.

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

The period of validity of this resolution is limited to 1 April 2024 as the final analysis from the IMpower010 study is expected for the endpoint of disease-free survival (DFS).

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

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

In order to allow consistent consideration of patient numbers, taking into account the resolutions made on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication of lung cancer, the incidence of 59,700 patients forecast by the Robert Koch Institute for 2022 is used for the present calculation[2].

This is lower than the number of 64,922 patients used by the pharmaceutical company.

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

1. The percentage of patients with NSCLC is 73.6 to 83.6%[3] (43,939 to 49,909).
2. The percentage of patients with NSCLC is subdivided by stage: IIA (2.2%), IIB (7.8%) to IIIA (12.3%). This results in a range of 9,794 to 11,125.
3. According to the pharmaceutical company, the percentage of patients after tumour resection is 58.2% (5,700 to 6,476). Of these, 87.4% to 89.7% received complete resection (4,982 to 5,808), according to the pharmaceutical company.

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

[3] Benefit assessment procedure D-832 selpercatinib; www.g-ba.de/bewertungsverfahren/nutzenbewertung/846

4. Adjuvant chemotherapy was received by 63.1% to 66.2% of resected patients (3,144 to 3,845), according to the pharmaceutical company.
5. According to the pharmaceutical company, the percentage of patients with EGFR mutation is 10.3% to 14.2% (324 to 546), and with ALK is 2% to 5.1% (63 to 196). Accordingly, the percentage of patients without EGFR and ALK mutations ranged from 2,757 to 3,103.
6. The percentage of patients with PD-L1 expression ≥ 50% is 28.9% (794 to 897), according to the pharmaceutical company.
7. Taking into account the percentage of SHI-insured patients of 88.3%[3], this results in 704 to 792 patients.

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

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Tecentriq (active ingredient: atezolizumab) at the following publicly accessible link (last access: 16 November 2022):

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.

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

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

- training material for health professionals

- patient pass

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 2022).

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

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

Based on the specifications in the product information, the treatment duration for adjuvant therapy with atezolizumab is limited to 12 months, but may be shorter on a patient-individual basis. Against this background, therefore, only the completed cycles in the treatment year are considered.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Atezolizumab	1 x every 14 days	26.1	1	26
	or			
	1 x every 21 days	17.4	1	17
	or			
	1 x every 28 days	13.0	1	13
Appropriate comparator therapy				
Monitoring wait-and-see approach		incalculable		

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treat-ment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Atezolizumab	840 mg	840 mg	1 x 840 mg	26	26 x 840 mg
	or				
	1200 mg	1200 mg	1 x 1200 mg	17	17 x 1200 mg
	or				

Designation of the therapy	Dosage/ application	Dose/ patient/ treat-ment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	1680 mg	1680 mg	2 x 840 mg	13	26 x 840 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	incalculable				

Costs:

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 840 mg	1 CIS	€ 2,923.44	€ 1.77	€ 163.67	€ 2,758.00
Atezolizumab 1,200 mg	1 CIS	€ 4,151.65	€ 1.77	€ 233.81	€ 3,916.07
Appropriate comparator therapy					
Monitoring wait-and-see approach	incalculable				
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 December 2022

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 had 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 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs 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 Hilfstaxe.

2.5 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 Atezolizumab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate 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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 21 April 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 4 July 2022, 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 4 July 2022, 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 11 October 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 17 October 2022. The deadline for submitting written statements was 7 November 2022.

The oral hearing was held on 21 November 2022.

By letter dated 22 November 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 8 December 2022.

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 20 December 2022, and the proposed resolution was approved.

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	21 April 2020	Determination of the appropriate comparator therapy
Working group Section 35a	15 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	21 November 2022	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	29 November 2022 13 December 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure

Subcommittee Medicinal products	20 December 2022	Concluding discussion of the draft resolution
Plenum	5 January 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 05 January 2023

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

Prof. Hecken