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 (reassessment after the deadline: non-small cell lung cancer, PD-L1 expression ≥ 50%, adjuvant therapy after resection and chemotherapy)

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. 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 pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient atezolizumab (Tecentriq) on 4 July 2022. For the resolution of 05 January 2023 made by the G-BA in this procedure, a limitation up to 1 April 2024 was pronounced. At the pharmaceutical company's request, this limitation was extended until 1 October 2024 by the resolution of the G-BA of 17 August 2023.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Tecentriq recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of

Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 26 September 2024.

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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of atezolizumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has 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.

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:

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; adjuvant treatment

Appropriate comparator therapy for atezolizumab as monotherapy:

Monitoring wait-and-see approach

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

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, medicinal products with the active ingredients pembrolizumab and vinorelbine are approved in the present 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. The G-BA therefore expects for the present treatment setting that radiotherapy is eligible only in individual cases for a few patients and is therefore not included among the standard therapies in the therapeutic indication.

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

- Pembrolizumab (resolution of 17 October 2024)
- Atezolizumab (resolution of 5 January 2023)

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

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V. No written opinions were received.

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

The recommendations in guidelines[2,3,4,5] on adjuvant therapy options are made, depending on the respective tumour stage.

The determination of the appropriate comparator therapy is based on the currently valid TNM tumour classification in the 8th edition of the UICC/AJCC[6].

There are changes to the stage classifications, particularly in stages IB and III, compared to the stage classification in the 7th edition of the UICC, on which the IMpower010 study was based. The appropriate comparator therapy was determined for stages II to IIIA according to the TNM tumour classification in the 8th edition of the UICC.

The S3 guideline recommends that patients with stage II or IIIA NSCLC (without EGFR or ALK alteration) after primary R0 resection and adjuvant chemotherapy with PD-L1 expression ≥ 50% should be offered adjuvant therapy with atezolizumab for 1 year. However, atezolizumab itself is excluded as an appropriate comparator therapy with regard to the research question of the benefit assessment since the present case concerns the determination of the appropriate comparator therapy for atezolizumab.

In addition, the immune checkpoint inhibitor pembrolizumab is available for the adjuvant treatment of patients with completely resected NSCLC (without EGFR or ALK alteration) and after platinum-based chemotherapy, regardless of PD-L1 expression

[2] Guideline programme in oncology; S3 guideline - Prevention, diagnosis, therapy and after-care of lung cancer, version 3.0 – March 2024; AWMF registry number: 020-007OL

[3] Daly ME et al., 2024. Management of Stage III Non-Small-Cell Lung Cancer: ASCO Guideline Rapid Recommendation Update.

[4] National Institute for Health and Care Excellence (NICE), 2019. Lung cancer: diagnosis and management.

[5] Pisters K et al., 2022. Adjuvant systemic therapy and adjuvant radiation therapy for stage I-IIIA completely resected non-small-cell lung cancer: ASCO Guideline Rapid Recommendation Update

[6] Union for International Cancer Control / American Joint Committee of Cancer

(marketing authorisation from 12.10.2023). An additional benefit of pembrolizumab compared to the monitoring wait-and-see approach was not proven in the benefit assessment (resolution of 17.10.2024). According to the current S3 guideline, adjuvant treatment with pembrolizumab should be offered, regardless of PD-L1 status. As background to this recommendation, the guideline states that the survival benefit in the pivotal study was very heterogeneous in the individual PD-L1 expression groups and also differed from studies of pembrolizumab in stage IV. In the cohort with PD-L1 expression ≥ 50%, the improvement in DFS was insignificant.[2]

In this regard, the joint statement of the Working Group for Internal Oncology of the German Cancer Society (AIO), the German Society for Haematology and Medical Oncology (DGHO) and the German Respiratory Society (DGP) on the present benefit assessment points out that a comparison with pembrolizumab would be formally possible due to the marketing authorisation, but that no significant difference was shown between pembrolizumab and placebo in the subgroup of patients with PD-L1 expression > 50%. In the statement, the appropriate comparator therapy of monitoring wait-and-see approach is considered appropriate.

In the overall assessment, the G-BA considered it appropriate to determine the monitoring wait-and-see approach as the appropriate comparator therapy for the present resolution on the new benefit assessment of atezolizumab in the therapeutic indication to be assessed after the expiry of the limitation. The monitoring wait-and-see approach is based in particular on appropriate after-care examinations, which are carried out in medical care after complete tumour resection.

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 considerable 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).

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. Overall, the sub-population includes 106 patients in the atezolizumab arm and 103 patients in the comparator arm.

In the IMpower010 study, the time between tumour resection and adjuvant chemotherapy was longer than 60 days for approx. 35% of patients. According to the guideline recommendation,[7] adjuvant chemotherapy should begin within 60 days of resection once wound healing is complete. Subgroup analyses by the pharmaceutical company for patients with ≤ 60 or > 60 days between tumour resection and adjuvant chemotherapy for the endpoints of overall survival and DFS showed no statistically significant effect modification. However, the benefit assessment points out that more pronounced effects were seen in the group of patients in whom adjuvant chemotherapy was started ≤ 60 days after tumour resection in accordance with the guidelines compared to the group of patients in whom more than 60 days elapsed between tumour resection and adjuvant chemotherapy.

For the ongoing IMpower010 study, 3 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))
- 26.01.2024 (interim analysis of overall survival after 316 events and final analysis of DFS after 240 events (planned after approximately 237 events))

For all endpoints, the pharmaceutical company uses the 3rd data cut-off for benefit assessment.

<u>On the implementation of the time limit requirements</u>

According to the justification of the resolution of 5 January 2025, the limitation was that further clinical data from the IMpower010 study were expected, which may be relevant for the benefit assessment. In particular, the data for the pre-specified final analysis of disease-free survival were not available at the time of the 2nd data cut-off of the IMpower010 study, which is why the significance of the study was considered limited and uncertainties remained.

For the new benefit assessment after expiry of the deadline, the IMpower010 study evaluations on all patient-relevant endpoints used for the evidence of an additional benefit should have been presented.

[7] Guideline programme in oncology; S3 guideline - Prevention, diagnosis, therapy and after-care of lung cancer, version 3.0 – March 2024; AWMF registry number: 020-007OL

The pharmaceutical company presented the required evaluations in the dossier, so that the time limit requirements are considered to have been implemented overall.

About the remaining 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 continues to be 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. According to the information provided by the pharmaceutical company from the written statement procedure, the percentage of patients in the assessment-relevant sub-population, who have stage IIIB tumours according to the current 8th classification, was 11%.

Overall, there continues to be 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.

Based on the information for the relevant sub-population on the subsequent therapies used after the end of the study medication, it is particularly striking that relatively few patients with recurrence received subsequent antineoplastic therapy in the comparator arm and that the percentage of checkpoint inhibitors as subsequent therapy was low. Subsequent therapy with checkpoint inhibitors in locally advanced or metastatic stage represents the current therapy standard. Overall, a relevant percentage of patients with relapse in the comparator arm of the IMpower010 study is to be assumed to have received inadequate subsequent therapy with respect to the therapy standard during the study period. In view of the size of the effect, the advantage of atezolizumab in the overall survival endpoint is not questioned, although its extent cannot be quantified with certainty.

Morbidity

Recurrences

The endpoint is represented by recurrence rate and disease-free survival, and includes the events of local recurrence, regional recurrence, distant recurrence, new primary NSCLC and death (without prior relapse).

The recurrence rate is defined as the percentage of patients who suffer a recurrence, a new primary NSCLC or die after complete tumour resection up to the present data cut-off. The first qualifying event is deemed to be an event.

Disease-free survival is defined as the time from randomisation until recurrence, new primary NSCLC or death, whichever occurs first.

In the unblinded IMpower010 study, disease-free survival was assessed by principal investigators. With study protocol version 9, a retrospective, blinded independent central review (BICR) by an independent review facility (IRF) was also made possible. This central review was available for around 94% of patients at the current data cut-off, which is why not all study participants were included in this assessment. Furthermore, this evaluation of the DFS in accordance with the BICR does not include a list of the individual qualifying events. However, the pre-specified evaluations by principal investigators were used for the present benefit assessment as the evaluations presented did not show any relevant differences between the assessment of DFS by BICR and by principal investigators.

Both endpoints (recurrence rates and disease-free survival) showed a statistically significant difference to the advantage of atezolizumab compared to the monitoring wait-and-see approach, the extent of which is assessed as significant improvement. The avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting. The (high) risk period is considered to be covered by the present observation period.

Quality of life

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

Side effects

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).

Therapy discontinuation due to AEs

For the endpoint of therapy discontinuation due to AEs, there was 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, AE), skin and subcutaneous tissue disorders (SOC, AEs), and infections and infestations (SOC, SAEs), atezolizumab showed a statistically significant disadvantage compared with the monitoring wait-and-see approach.

In summary, a disadvantage of treatment with atezolizumab due to negative effects in SAEs and therapy discontinuation due to AEs was identified in the endpoint category of side effects. With regard to specific adverse events, there were disadvantages of atezolizumab, in detail.

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. In view of the size of the effect, the advantage of atezolizumab in the overall survival endpoint is not questioned, although its extent cannot be quantified with certainty.

With regard to the results on recurrences, presented as recurrence rate and disease-free survival, an advantage of atezolizumab compared to the monitoring wait-and-see approach was identified, the extent of which is assessed as significant improvement. The avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting.

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

In terms of side effects, there was a disadvantage of treatment with atezolizumab due to negative effects in SAEs and therapy discontinuation due to AEs. With regard to specific adverse events, there were disadvantages of atezolizumab, in detail.

In the overall analysis, the advantage in overall survival and the significant advantage in the endpoint of recurrences are offset by disadvantages in terms of side effects. These disadvantages are weighted against the background of the present curative therapeutic approach and do not question the extent of improvement in the overall assessment.

As a result, 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 ≥ 50% of tumour cells (TC) and do not have EGFR-mutated or ALK-positive NSCLC is found to have a considerable 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 the endpoint of recurrences, the risk of bias is rated to be low.

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

For therapy 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 for the overall assessment of the additional benefit is limited by the fact 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 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient atezolizumab due to the expiry of the limitation of the resolution of 5 January 2023.

The therapeutic indication assessed here is as follows:

"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".

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. Uncertainties arise due to inadequate subsequent therapies in the comparator arm.

Considering the present curative therapeutic approach, the avoidance of recurrences represents a significant therapeutic goal. The results for the endpoints of recurrence rate and disease-free survival showed a statistically significant advantage of atezolizumab.

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

In terms of side effects, there was a disadvantage of treatment with atezolizumab due to negative effects in SAEs and therapy discontinuation due to AEs. With regard to specific adverse events, there were disadvantages of atezolizumab, in detail.

In the overall analysis, the advantage in overall survival and the significant advantage in the endpoint of recurrences are offset by disadvantages in terms of side effects. These disadvantages are weighted against the background of the present curative therapeutic approach and do not question the extent of improvement in the overall assessment.

A considerable additional benefit of atezolizumab over the monitoring wait-and-see approach is identified as a result.

Overall, this results in 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 in some patients was not in accordance with the guideline and some 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.

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

The resolution is based on information provided by the pharmaceutical company in the dossier on the benefit assessment.

The pharmaceutical company's calculation includes over- or underestimations, which are associated with uncertainties. Overall, the pharmaceutical company's derivation of the patient numbers is largely plausible.

Uncertainties arise, among other things, from the fact that the pharmaceutical company refers to the 7th edition of the UICC when deriving the patient numbers. The now 8th UICC edition results in some changes to the stage classifications and the percentages for the individual stages, which affect several derivation steps, in particular the number of patients with NSCLC at high risk of recurrence according to the product information.

In the publication (Kraywinkel et al. (2018)) on the classification of tumour stages according to the UICC used by the pharmaceutical company to calculate the percentage of patients at high risk of recurrence, it was only possible to classify the tumour stages in around 80% of NSCLC cases. The percentage values per stage might have been different if information had been available for those cases with unknown UICC stage.

There are uncertainties with regard to the percentage of patients with anatomical lung resection, as the percentage values used refer to all primary cases of lung cancer without limitation to NSCLC.

Further uncertainties arise from the deduction of the number of patients with EGFR mutation or with ALK-positive NSCLC, as both percentage estimates relate to different stages of the disease, among other things.

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 March 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.

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

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. 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 requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 March 2025).

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

Based on the requirements 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 per 21-day cycle	17.4	1	17
Appropriate comparator therapy				
Monitoring wait-and-see approach		Not calculable		

Consumption:

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	17.0	17 x 1,875 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach		Not calculable			

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. 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					
Monitoring wait-and-see approach	Not calculable				
Abbreviations: SFI = solution for injection					

LAUER-TAXE® last revised: 1 March 2025

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.

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:

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; adjuvant treatment

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.

Product information for atezolizumab (Tecentriq); Tecentriq 840 mg/ 1,200 mg; last revised: December 2024

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

On 26 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 5 VerfO.

By letter dated 27 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 18 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.

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	21 April 2020	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
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