

Justification



to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Atezolizumab (New Therapeutic Indication: Advanced Small Cell Lung Cancer, First Line, Combination with Carboplatin and Etoposide)

of 2 April 2020

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1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient atezolizumab (Tecentriq®) was listed for the first time on 15 October 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 3 September 2019, atezolizumab received marketing authorisation for a new therapeutic indication:

"Tecentriq®, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)."

On 2 October 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient atezolizumab with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 15 January 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

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

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of atezolizumab (Tecentriq®) in accordance with the product information

Tecentriq®, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

2.1.2 Appropriate comparator therapy

Adult patients with extensive-stage small cell lung cancer (ES-SCLC); first-line treatment

Appropriate comparator therapy:

- Cisplatin and etoposide

or

- Carboplatin and etoposide

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

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.

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

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

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

- On 1. Medicinal products with the following active ingredients are approved for the present therapeutic indication:

Carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, etoposide, ifosfamide, lomustine, and vincristine.

- On 2. In the present therapeutic indication, prophylactic cranial irradiation (PCI) and radiotherapy are generally considered as non-medicinal treatment options.

Based on the evidence available, PCI is recommended for those patients who have responded to first-line chemotherapy. PCI is therefore a treatment option applied after first-line chemotherapy in the case of complete or partial remission. In addition, according to the guideline recommendations, other radiotherapeutic interventions are, in principle, possible. The early application of cranial irradiation is recommended for patients with initial brain metastasis, for patients with very good remission of distant metastasis also primary tumour irradiation is recommended, for patients with need a symptom-oriented, palliative irradiation mainly for pain relief or prevention of complications is recommended.

The aforementioned radiotherapeutic interventions are therefore either applied after first-line chemotherapy (and depending on the response to it) or are considered only for a part of the patients in the therapeutic indication. They are therefore not determined as an appropriate comparator therapy. Their use as an additional therapeutic option remains unaffected.

- On 3. The following resolutions or guidelines of the G-BA are available for medicinal applications:

Annex VI to Section K of the Pharmaceuticals Directive – Prescribability of authorised medicinal products in non-approved therapeutic indications – Part A: Irinotecan for small cell lung cancer (SCLC), extensive disease.

- On 4. The generally state of medical knowledge for the indication was established by means of a systematic search for guidelines and reviews of clinical studies.

In these guidelines, the use of etoposide in combination with either cisplatin or carboplatin is consistently recommended for the first-line treatment of small cell lung cancer in the extensive stage. In accordance with the S3 guideline, cisplatin and carboplatin can be considered equally effective, although carboplatin is preferred because of its lower rate of side effects. In contrast, other guidelines do not differentiate between carboplatin and cisplatin in their therapy recommendations.

Furthermore, there are sometimes weaker recommendations for irinotecan in combination with a platinum derivative (cisplatin or carboplatin). Although not approved in the present therapeutic indication, irinotecan is prescribable according to Annex VI to Section K of the Pharmaceuticals Directive (see 3.). However, the prescribability of irinotecan with a platinum preparation is only available for patients who have received a platinum preparation and etoposide in first-line therapy and in whom such serious etoposide-related side effects have been observed that continued administration of etoposide would be associated with unacceptable risks. A

combination therapy of irinotecan and a platinum preparation can therefore not be considered as an appropriate comparator therapy for the present therapeutic indication.

In the overall view, the combination therapies cisplatin and etoposide or carboplatin and etoposide are therefore determined as equally appropriate comparator therapies.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of atezolizumab in combination with carboplatin and etoposide is assessed as follows:

Hint for a minor additional benefit.

Justification:

The pharmaceutical company submitted data on the benefit assessment from the ongoing randomised, double-blind, placebo-controlled IMpower133 Phase III study.

In main cohort (global cohort) of the IMpower133 study, 403 adult patients with advanced small cell lung cancer (ES-SCLC) and an ECOG-PS ≤ 1 , were enrolled at the start of study. Patients with brain metastases were enrolled if they were treated and asymptomatic at the time of inclusion. In the IMpower133 study, the proportion of these patients was only 8.5% in the intervention arm and 8.9% in the comparator arm. Patients with untreated or symptomatic brain metastases as well as patients with an ECOG-PS ≥ 2 were disqualified. Symptomatic brain metastases include both uncontrolled brain metastases (i.e. with cerebral pressure signs) for which therapy with PD-L1 inhibitors is not recommended and symptomatic but controlled brain metastases (e.g. with focal neurological focal symptoms but without cerebral pressure), for which therapy with PD-L1 inhibitors is not excluded *per se* according to the clinical experts. The patients were randomised at a ratio of 1:1 and stratified according to ECOG-PS, sex, and the presence of brain metastases.

Patients in the intervention arm received a total of four cycles of atezolizumab in combination with carboplatin and etoposide followed by maintenance treatment with atezolizumab alone. The patients of the comparator arm received carboplatin in combination with etoposide and placebo for four cycles followed by maintenance treatment with placebo.

The co-primary endpoints of the study are progression-free survival (PFS) and overall survival. Patient-relevant secondary endpoints are symptomatology, health status, health-related quality of life, and adverse events.

Treatment was continued until disease progression, unacceptable toxicity, start of another tumour therapy, withdrawal of informed consent, or death. Atezolizumab may continue to be administered at the discretion of the investigator even after progression provided there is continued clinical benefit. There are no restrictions with regard to treatment after the end of the study medication.

In addition to the global cohort, another cohort in China (Chinese cohort) with the same study protocol will be investigated. The cohort in China comprises a total of 110 patients, 57 of whom are assigned to the intervention arm and 53 to the control arm. This cohort was recruited after the recruitment phase of the global cohort was completed, according to the statement of the pharmaceutical company for the purpose of marketing authorisation in China.

The pharmaceutical company did not use the results of the Chinese cohort to derive an additional benefit citing regulatory reasons, different baseline characteristics compared with the global cohort and a lack of transferability to the local healthcare context. However, these were additionally presented in Module 4 of the benefit assessment dossier.

However, the results for the global cohort and the Chinese cohort were summarised meta-analytically by IQWiG as part of the dossier evaluation. On one hand, because no effect modification by the characteristic descent was shown in the subgroup analyses carried out by the pharmaceutical company for the efficacy endpoints. On the other hand, because no statistically significant heterogeneity between the results was observed in the meta-analyses.

In the written statement procedure, the relevance of the Chinese cohort for the present benefit assessment was assessed differently by the medical societies. On the one hand, in view of different baseline characteristics between the two cohorts (e.g. with regard to age, sex, proportion of never-smokers, and patients with brain metastases) and limited comparability of medical care standards, a meta-analytical inclusion of the Chinese cohort in the benefit assessment was described as difficult to comprehend. On the other hand, the need to consider as much evidence as possible in order to avoid bias through data selection – in particular because the relatively high proportion of the Chinese cohort in the total population of 20% – was pointed out.

In its overall assessment of the relevance of the Chinese cohort, the G-BA considers it appropriate to include it in the assessment in the present case. This is based on the fact that the Chinese cohort is initially suitable in principle to answer the question of the benefit assessment by assessing the additional benefit of atezolizumab in combination with carboplatin and etoposide. Furthermore, as described above, no effect modification by the characteristic parentage was found in the sub-group analyses for the efficacy endpoints, and no statistically significant heterogeneity between results was found in any of the meta-analyses conducted by IQWiG. In addition, the Chinese cohort, with 20% of the total study population, contributes significantly to the evidence available.

For the present assessment, the meta-analytical summary of the results of the two cohorts of the IMpower133 study, if available, is used. Several data cut-offs are available for both cohorts. For the global cohort a first data cut-off of 24 April 2018 is available for the primary analysis of the PFS and for the interim analysis of overall survival. In addition, results of a second data cut-off of 24 January 2019, which was originally planned as final analysis of overall survival but was requested by the EMA as part of the approval process. For the Chinese cohort the first data cut-off of 29 October 2018 corresponds to the planned primary analysis of the PFS. The second data cut-off of 24 January 2019 corresponds to the first interim analysis on overall survival. In addition, a third data cut-off of 31 July 2019 was submitted by the pharmaceutical company for the Chinese cohort as part of the written statement procedure. According to the pharmaceutical company, this is the basis for the marketing authorisation in China.

For overall survival, the present benefit assessment is based on the results of the data cut-off of 24 January 2019 for the global cohort and the data cut-off of 31 July 2019 for the Chinese cohort; for the side effects endpoints (except for the specific AE), on the results of the data cut-off of 24 April 2018 for the global cohort and the data cut-off of 31 July 2019 for the Chinese cohort; for specific AE, on the results of the data cut-off of 24 April 2018 for the global cohort and the data cut-off of 24 January 2019 for the Chinese cohort; for the remaining endpoints, on the on the results of the data cut-off of 24 April 2018 for the global cohort and the data cut-off of 29 October 2018 for the Chinese cohort.

Extent and probability of the additional benefit

Mortality

In the IMpower133 study, overall survival is defined as the time from randomisation to death by any cause. In the global cohort, 142 patients (70.6%) in the intervention arm and 160

patients (79.2%) in the comparator arm had died by the data cut-off of 24 January 2019. Within the Chinese cohort, 41 patients each (71.9% vs 77.4%) died in the intervention arm and control arm at the data cut-off of 31 July 2019.

The meta-analysis of the event time analyses for both study cohorts shows a statistically significant difference in favour of atezolizumab in combination with carboplatin and etoposide compared with carboplatin in combination with etoposide (HR: 0.79 [95% CI: 0.65; 0.97], $p = 0.026$).

In the endpoint category mortality, based on the results of the IMpower133 study, there is a small prolongation of overall survival and thus a minor additional benefit.

Morbidity

Progression-free survival (PFS)

The PFS is a co-primary endpoint of the IMpower133 study and is operationalised as the time between randomisation and the time of first disease progression after RECIST or death by any cause. At the time of the first data cut-off in the intervention arm of the global cohort, the PFS was statistically significantly prolonged by 0.9 months (median) compared with the control arm (5.2 vs 4.3 months (median)); (HR: 0.77 [0.62; 0.96]; $p < 0.017$). In the Chinese cohort, there was no statistically significant difference between treatment groups at the time of the first data cut-off. A meta-analytical summary of the cohorts is not available.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” is collected as an independent endpoint via the endpoint overall survival. The morbidity component is not surveyed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology

In the IMpower133 study, the symptomatology of the patients is assessed by the symptom scales of the EORTC-QLQ-C30 and EORTC-QLQ-LC13 questionnaires.

In the meta-analytical summary of the responder analyses for the time to deterioration by at least 10 points from the baseline, there is no statistically significant difference between the treatment groups in any symptom scale.

Health status (EQ-5D visual analogue scale)

In order to evaluate the health status of the study patients, the pharmaceutical company presents responder analyses for the time to first deterioration by at least 10 points compared with baseline.

Instead of the responder analyses, the dossier evaluation of the IQWiG uses analyses of mean differences. The difference between the study arms is not statistically significant regarding mean difference.

The IQWiG classifies the study on which the derivation of the MID for the responder analyses is based (Pickard et al., 2007) as unsuitable to prove the validity of the MID. This is justified on one hand by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID. In addition, the IQWiG does not consider the ECOG-PS and FACT-G anchors used in the study to be suitable for the derivation of MID.

Against the background that responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with an analysis of standardised mean differences and taking into account that the validation study in question has already been used in earlier evaluations, the G-BA nevertheless uses the responder analyses in the present assessment to assess the effects on symptomatology.

In the meta-analysis of the event time analyses, there was no statistically significant difference between the treatment groups.

Overall, there is no additional benefit in terms of symptomatology and health status from treatment with atezolizumab in combination with carboplatin and etoposide.

Quality of life

In the IMpower133 study, the health-related quality of life is reported by the patients and is assessed using the functional scales of the EORTC-QLQ-C30 questionnaire.

In the meta-analytical summary of the responder analyses for the time to deterioration by at least 10 points from the baseline, there is no statistically significant difference between the treatment groups in any functional scale.

Side effects

Adverse events (AE) in total

In the IMpower133 study, almost all patients in the intervention and control arms of both cohorts experienced an adverse event. The results for the endpoint “total adverse events” are only presented on a supplementary basis.

Serious AE

In the global cohort of the IMpower133 study, approx. 37% of the patients in the intervention arm and approx. 35% of the patients in the comparator arm experienced a serious adverse event. For the Chinese cohort, the proportion is about 37% for the intervention arm and about 27% for the reference arm. In the meta-analysis of the event time analyses for both study cohorts, no statistically significant difference was found.

Severe AE (CTCAE grade ≥ 3)

A severe adverse event (CTCAE grade ≥ 3) was experienced by approximately 69% of patients in the intervention and comparator arm of the global cohort. For the Chinese cohort, the proportion is about 81% for the intervention arm and about 83% for the reference arm. In the meta-analysis of the event time analyses for both study cohorts, no statistically significant difference was found.

Therapy discontinuation because of AE

In the global cohort, approx. 11% of patients in the intervention and 3% in the comparator arm discontinued treatment because of adverse events. In the Chinese cohort, approx. 12% of patients in the intervention arm discontinued treatment because adverse events; in the comparator arm, no patients discontinued treatment. Thus, no effect estimator can be calculated for the Chinese cohort, and a meta-analytical evaluation for both cohorts is not available. The assessment is therefore based on the event time analysis for the global cohort. There is a statistically significant difference between the treatment groups to the disadvantage of atezolizumab in combination with carboplatin and etoposide.

In this context, the estimation on this endpoint presented by the pharmaceutical company in the written statement (i.e. that the statistically significant difference to the disadvantage of atezolizumab in combination with carboplatin and etoposide is not relevant to the patient in the present case because in most cases, only the additional administration of atezolizumab or placebo was discontinued) is not followed. Discontinuation of one component of a treatment regimen is also due to the occurrence of such a significant adverse event that treatment is no longer tolerated and must be discontinued. This discontinuation, as an indicator for the occurrence of a significant adverse event, thus represents a patient-relevant event.

Specific AE

Because the pharmaceutical company did not submit all the event time analyses required for a complete consideration of specific AE, especially for the Chinese cohort, the assessment is based on relative risks in order to allow a common view for both cohorts.

In the area of specific adverse events, there are statistically significant differences to the disadvantage of atezolizumab in combination with carboplatin and etoposide regarding immune mediated AE, immune mediated serious AE, and immune mediated severe AE (CTCAE grade 3 and 4).

Overall, the results on side effects show negative effects for atezolizumab in combination with carboplatin and etoposide compared with carboplatin in combination with etoposide because of an increase in therapy discontinuations because of AE. In detail, negative effects can also be seen in the area of specific AE through an increase in immune mediated AE, immune mediated serious AE, and immune mediated severe AE (CTCAE grade 3 and 4).

Overall assessment

For the benefit assessment of atezolizumab in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), the results on overall survival, morbidity, health-related quality of life, and side effects from the Impower133 study are available. Where possible, the assessment is based on the meta-analytical summary of the results of the two cohorts examined in this study (global and Chinese cohort).

In the endpoint category mortality, there was a statistically significant difference between the treatment arms. Compared with carboplatin in combination with etoposide, atezolizumab in combination with carboplatin and etoposide leads to a slight prolongation of overall survival; this is classified as a minor additional benefit.

There are no differences in morbidity surveyed by the EORTC-QLQ-C30 and EORTC-QLQ-LC13 measuring instruments or the visual analogue scale of EQ-5D. In particular, there were no advantages regarding the effects on disease-specific symptoms. The symptomatology of advanced SCLC is usually pronounced and stressful for the patient. Effects on the symptomatology are therefore significant for the patients.

Also with regard to health-related quality of life, the EORTC-QLQ-C30 functional scales show no differences between the treatment arms.

On the other hand, there are disadvantages in terms of discontinuations because of AE; in addition, in the area of specific AE in detail, there is an increase in immune mediated AE, immune mediated serious AE, and immune mediated severe AE (CTCAE grade 3 and 4).

The overall assessment concludes that the positive effect on overall survival is not supported by other positive effects on patient-relevant outcomes but rather that the disadvantages for side effects do not fully compensate for this positive effect. In a balancing decision, the G-BA has concluded that the advantages with respect to overall survival outweigh the disadvantages. Therefore, for atezolizumab in combination with carboplatin and etoposide for

the first-line treatment of adult patients with extensive-stage small cell lung cancer, there is a minor additional benefit compared with carboplatin in combination with etoposide.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, double-blind, placebo-controlled, Phase III IMpower133 study. The risk of bias at the study level is classified as low.

At the endpoint level, the bias risk of bias for the endpoints overall survival and therapy discontinuation because of AE is considered low. However, assessment-relevant uncertainties arise from the fact that the proportion of patients with brain metastases included in the study was very low and that no data are available on patients with symptomatic brain metastases. Because the incidence of brain metastases in small cell lung cancer is already particularly high initially and is particularly relevant for the course of the disease, this fact is of particular importance.

Furthermore, for the endpoints on side effects, sub-group analyses are available only for the characteristics age and sex but not for the other relevant sub-group characteristics (descent, smoker status, and brain metastases).

In the overall view, the uncertainties described justify a classification of the reliability of data as a hint for an additional benefit.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient atezolizumab:

“Tecentriq®, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).”

Cisplatin and etoposide or carboplatin and etoposide were determined as an appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company presents the results of the randomised, double-blind, placebo-controlled IMpower133 study in which atezolizumab in combination with carboplatinum and etoposide is compared with carboplatinum in combination with etoposide. The IMpower133 study examines two cohorts (global and Chinese cohort), which were meta-analytically combined for the assessment where possible.

In the endpoint category mortality, a statistically significant difference is shown for the endpoint overall survival in the meta-analysis of the event time analyses for both cohorts. Atezolizumab in combination with carboplatin and etoposide leads to a prolongation of overall survival; this can be classified as a minor additional benefit.

There are no statistically significant differences for the patient-reported morbidity endpoints. In particular, there are no advantages regarding the effects on disease-specific symptoms. Likewise, neither advantageous nor disadvantageous effects are shown in the endpoint category quality of life.

In the endpoint category side effects, there are statistically significant differences to the detriment of atezolizumab in combination with carboplatin and etoposide for therapy discontinuation because of AE. In addition, disadvantages in the area of specific AE are shown in detail by an increase in immune mediated AE.

In a balancing decision, the G-BA has concluded that the advantages with respect to overall survival, which is not supported by other positive effects on patient-relevant outcomes, does,

however, outweigh the disadvantages. There is thus a minor additional benefit compared with carboplatin in combination with etoposide.

There are uncertainties because of the under-representation of patients with brain metastases, the complete lack of data on patients with symptomatic brain metastases in the study, and the lack of sub-group analyses in the endpoint category side effects. Therefore, the overall data is limited. As a result, only a hint for an additional benefit can be derived with regard to the reliability of data.

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 G-BA bases its resolution on the information from the dossier of the pharmaceutical company. The calculation used to derive patient numbers is comprehensible, and the magnitude of the figures arrived at are largely plausible. The stated range reflects the minimum and maximum values obtained when deriving the patient numbers.

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: 10 December 2019):

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

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

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

- Training material for health professionals
- Patient pass

The training material includes, in particular, instructions on how to deal with the immune mediated side effects potentially occurring under atezolizumab treatment as well as infusion-related reactions.

Patients with symptomatic brain metastases were disqualified from the IMpower133 study. Thus, no data are available for patients with symptomatic brain metastases.

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: 15 March 2020).

According to the product information, the recommended dose of atezolizumab in combination therapy with carboplatin and etoposide during the induction phase is 1,200 mg every three weeks for four cycles. The induction phase is followed by a maintenance phase without

chemotherapy; during this phase, Tecentriq (1,200 mg) is administered intravenously every three weeks.

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

For dosages depending on body weight (BW) or body surface, the average body measurements were used as a basis (average body size: 1.72 m, average body weight: 77 kg).² From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916)

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
<i>Induction therapy</i>				
Atezolizumab	1 x per 21-day cycle	4	1	4
Carboplatin	1 x per 21-day cycle	4	1	4
Etoposide	On Day 1–3 of a 21-day cycle	4	3	12
<i>Maintenance treatment</i>				
Atezolizumab	1 x per 21-day cycle	13.4 cycles	1	13.4
Appropriate comparator therapy				
Cisplatin + etoposide				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Etoposide	On Day 1–3 of a 21-day cycle	17.4	3	52.2
Carboplatin + etoposide				
Carboplatin	1 x per 21-day cycle	17.4	1	17.4

² German Federal Office For Statistics, Wiesbaden 2018: <http://www.gbe-bund.de/>

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Etoposide	On Day 1–3 of a 21-day cycle	17.4	3	52.2

Usage and 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					
<i>Induction therapy</i>					
Atezolizumab	1200 mg	1200 mg	1 × 1200 mg	4	4 × 1200 mg
Carboplatin	400 mg/m ² = 760 mg	760 mg	2 × 150 mg +	4	8 × 450 mg +
			1 × 600 mg	4	4 × 600 mg
Etoposide	100 mg/m ² = 190 mg	190 mg	1 × 200 mg	12	12 × 200 mg
<i>Maintenance treatment</i>					
Atezolizumab	1200 mg	1200 mg	1 × 1200 mg	13.4	13.4 × 1200 mg
Appropriate comparator therapy					
Cisplatin + etoposide ³					
Cisplatin	75 mg/m ² = 142.5 mg	142.5 mg	1 × 100 mg +	17.4	17.4 × 100 mg +
			1 × 50 mg		17.4 × 50 mg
Etoposide	100 mg/m ² = 190 mg	190 mg	1 × 200 mg	52.2	52.2 × 200 mg
Carboplatin + etoposide ⁴					

³ Belani CP, Lee JS, Socinski MA, Robert F, Waterhouse D, Rowland K et al. Randomised Phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. *Ann Oncol* 2005; 16(7): 1069–1075

⁴ Socinski, Mark & Smit, Egbert & Lorigan, Paul & Konduri, Kartik & Reck, Martin & Szczesna, Aleksandra & Blakely, Johnetta & Serwatowski, Piotr & Karaseva, Nina & Ciuleanu, Tudor & Jassem, Jacek & Dediu, Mircea & Hong, Shengyan & Visseren-Grul, Carla & Hanauske, Axel-Rainer &

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/patient/year	Average annual consumption by potency
Carboplatin	400 mg/m ² = 760 mg	760 mg	2 x 150 mg	17.4	34.8 x 450 mg
			1 x 600 mg		17.4 x 600 mg
Etoposide	100 mg/m ² = 190 mg	190 mg	1 x 200 mg	52.2	52.2 x 200 mg

Costs:

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

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Atezolizumab 1200 mg	1 CIS	€ 4,692.05	€ 1.77	€ 264.69	€ 4,425.59
Carboplatin 150 mg	1 CIS	€ 82.79	€ 1.77	€ 3.40	€ 77.62
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Etoposide 200 mg	1 CIS	€ 81.62	€ 1.77	€ 3.35	€ 76.50
Appropriate comparator therapy					
Carboplatin 150 mg	1 CIS	€ 82.79	€ 1.77	€ 3.40	€ 77.62
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Cisplatin 100 mg	1 CIS	€ 76.31	€ 1.77	€ 3.10	€ 71.44

Obasaju, Coleman & Guba, Susan & Thatcher, Nick. (2009). Phase III Study of Pemetrexed Plus Carboplatin Compared With Etoposide Plus Carboplatin in Chemotherapy-Naive Patients With Extensive-Stage small cell Lung Cancer. *Journal of clinical oncology* : official journal of the American Society of Clinical Oncology. 27. 4787–92. 10.1200/JCO.2009.23.1548.

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Cisplatin 50 mg	1 CIS	€47.43	€1.77	€1.73	€43.93
Etoposide 200 mg	1 CIS	€81.62	€1.77	€3.35	€76.50
Abbreviations: CIS = Concentrate for the preparation of an infusion solution					

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

Costs for additionally required SHI services:

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

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

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

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/year	Costs/patient/year
Appropriate comparator therapy							
Cisplatin							
Anti-emetic treatment							
In clinical practice, appropriate anti-emetic treatment is established before and/or after cisplatin administration. The product information of cisplatin does not contain any concrete information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% infusion solution, 37.5 g/day	10 × 500 ml	€106.22	€5.31	€9.81	€91.10	17.4	€158.51

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/year	Costs/patient/year
Sodium chloride 0.9% infusion solution, 3–4.4 l/day	10 x 1,000 ml	€ 35.47	€ 1.77	€ 1.12	€ 32.58	17.4	€ 170.07 –
	10 x 500 ml	€ 22.72	€ 1.14	€ 0.69	€ 20.89		€ 263.11

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

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

3. Bureaucratic costs

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 February 2019.

On 2 October 2019, the pharmaceutical company submitted a dossier for the benefit assessment of atezolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 7 October 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal

products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient atezolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 January 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 January 2020. The deadline for submitting written statements was 5 February 2020.

The oral hearing was held on 24 February 2020.

By letter dated 25 February 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 13 March 2020.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 24 March 2020, and the proposed resolution was approved.

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

The patient representatives support the resolution.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	12 February 2019	Determination of the appropriate comparator therapy
Working group Section 35a	19 February 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	24 February 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 March 2020 18 March 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	24 March 2020	Concluding discussion of the draft resolution
Plenum	2 April 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 April 2020

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

Prof. Hecken