Justification

Gemeinsamer Bundesausschuss

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

of 2 April 2020

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

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

On 3 September 2019, atezolizumab received marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 25 September 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 “Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC” 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 2 January 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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

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

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

Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy:

- Pembrolizumab as monotherapy

b) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

Appropriate comparator therapy:

- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)

or

- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) *cf* Annex VI to Section K of the Pharmaceuticals Directive

or

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

- Carboplatin in combination with nab-paclitaxel

or

- Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy

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

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

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

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

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

On 1. With regard to the authorisation status, the active ingredients bevacizumab, cisplatin, crizotinib, dabrafenib, docetaxel, gemcitabine, ifosfamide, mitomycin, nab-paclitaxel, paclitaxel, pembrolizumab, pemetrexed, trametinib, vindesine, and vinorelbine are available for the first-line treatment of metastatic non-squamous, non-small cell lung cancer (NSCLC) and without EGFR and ALK-positive tumour mutations. In addition, carboplatinum can be prescribed for off-label use in this therapeutic indication.

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

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

On 3. For the therapeutic indication of atezolizumab, the following G-BA resolutions or guidelines are available for medicinal or non-medicinal treatments:

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

- Pembrolizumab (NSCLC, combination therapy): Resolution of 19 September 2019
- Dabrafenib (NSCLC with BRAF-V600 mutation): Resolution of 19 October 2017
- Trametinib (NSCLC with BRAF-V600 mutation): Resolution of 19 October 2017
- Pembrolizumab (PD-L1 expression: TPS ≥ 50%): Resolution of 3 August 2017
- Crizotinib (ROS1-positive NSCLC): Resolution of 16 March 2017

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

On 4. The general state of medical knowledge on which the findings of the G-BA are based was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

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

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

Current guidelines recommend a monotherapy with pembrolizumab for the first-line treatment of metastatic non-small cell lung cancer with a PD-L1 expression of ≥ 50%. The benefit assessment of pembrolizumab as monotherapy based on data from the Keynote-024 study showed an indication of a considerable additional benefit compared with platinum-based chemotherapy (resolution of 3 August 2017). Pembrolizumab significantly improved overall survival and delayed the occurrence of severe AE. There were also beneficial effects for health-related quality of life; significant disease symptoms occurred later. Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy was evaluated by the G-BA in its resolution of 19 September 2019 for the patient group with a PD-L1 expression of ≥ 50% (TPS) based on an adjusted indirect comparison to pembrolizumab monotherapy. Because the extent of the additional benefit observed in the overall survival endpoint cannot be quantified for the entire sub-population and an assessment of symptomatology and health-related quality of life is not possible, an additional benefit was identified; however, the extent of this is non-quantifiable. On the basis of this data, the G-BA defines pembrolizumab as monotherapy as the only appropriate comparator therapy for the first-line treatment of patients with PD-L1 expression ≥ 50% (TPS).

b) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

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

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

Within the scope of the benefit assessment, for pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy, a hint for a non-quantifiable additional benefit was issued in the resolution of 19 September 2019. For patients with a PD-L1 expression of < 50% (TPS), a hint for a non-quantifiable additional benefit compared with pemetrexed plus platinum-containing chemotherapy was found based on a meta-analysis of the two randomised and controlled Keynote-021G and Keynote-189 studies. An advantage was shown in the overall survival endpoint. However, the extent of this was non-quantifiable because of the subgroup analyses available and their

relevant uncertainties. When determining the present appropriate comparator therapy, it is taken into account that a meta-analysis of two randomised controlled trials forms the data basis for this sub-population. Furthermore, in the statements on the present benefit assessment, clinical experts stated that pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy represents a further standard of care. The G-BA therefore considers this therapeutic option to be another useful therapeutic option in the present therapeutic indication.

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

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

Because, atezolizumab in combination with nab-paclitaxel and carboplatin is used in this therapeutic indication, it can be assumed that the patients are generally suitable for combination chemotherapy so that mono-chemotherapies such as gemcitabine or vinorelbine cannot be considered as an appropriate comparator therapy.

In the overall view, the G-BA determined cisplatin or carboplatin in combination with a third-generation cytostatic drug or pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy to be equally appropriate comparator therapies for patients with a tumour proportion score [TPS] of < 50% (PD-L1 expression).

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

Change of the appropriate comparator therapy:

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

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

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

2.1.3 Extent and probability of the additional benefit

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

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

An additional benefit is not proven.

Justification:

For the first-line treatment of patients with a TPS of ≥ 50%, non-squamous histology, and without EGFR- or ALK-positive tumour mutations, no data were presented to assess the additional benefit of atezolizumab in combination with nab-paclitaxel and carboplatin compared with the appropriate comparator therapy.

b) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company presents the data of the ongoing, open-label, randomised IMpower130 Phase III study. In the IMpower130 study atezolizumab + nab-paclitaxel + carboplatin was compared with nab-paclitaxel + carboplatin. The study is being conducted in 131 centres in Europe and North America.

The study included adult patients with histologically or cytologically confirmed non-squamous NSCLC stage IV who had not previously received therapy for stage IV and had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1. The enrolment of the patients in the study was independent of the PD-L1 expression level in the tumour tissue as well as the EGFR and ALK status; however, these had to be known at the time of inclusion.

A total of 723 patients were randomised at a ratio of 2:1 to the two study arms (atezolizumab in combination with nab-paclitaxel and carboplatin: N = 483; nab-paclitaxel in combination with carboplatin: N = 240). In the IMpower130 study, patients were stratified according to sex, presence of liver metastases at baseline, and PD-L1 expression status in accordance with immunohistochemistry (IHC).

PD-L1 expression in tumour tissue was determined by the proportion of PD-L1 positive tumour cells (TC) and PD-L1 positive immune cells (IC). A PD-L1 expression of TC0/1/2 and IC0/1/2 is considered by the pharmaceutical company to be an approximation of a Tumour Proportion Score (TPS) < 50%. Complementary to this, a PD-L1 expression of TC3 or IC3 is evaluated by the pharmaceutical company to be an approximation of a PD-L1 expression ≥ 50% in accordance with TPS. It is viewed critically that a comprehensible and sound justification of the extent to which, in particular, a PD-L1 expression of IC3 actually corresponds to an approximation to a TPS ≥ 50% was not submitted by the pharmaceutical company. However, because in the present case, the proportion of patients with only IC3 (without TC3) is low (5.3% of the study population), the distribution of patients (PD-L1 expression < 50% = TC0/1/2 and IC0/1/2; PD-L1 expression ≥ 50% = TC3 and IC3) performed by the pharmaceutical company is used for the present benefit assessment.

The pharmaceutical company submits the results for two sub-populations in the dossier. The sub-population relevant for the benefit assessment is the NEoM population (patients without EGFR- or ALK-positive tumour mutations and an approximate PD-L1 expression of < 50% in accordance with TPS (TC0/1/2 and IC0/1/2); N = 554: atezolizumab + nab-paclitaxel + carboplatin: N = 368, nab-paclitaxel + carboplatin: N= 186). In addition, the pharmaceutical company presents the results of the wild type (WT) population. The WT population (N = 685; atezolizumab + nab-paclitaxel + carboplatin: N = 456; nab-paclitaxel + carboplatin: N = 229) includes patients without EGFR- or ALK-positive tumour mutations including patients with an approximate PD-L1 expression ≥ 50% TPS.

The treatment with the study medication was carried out in according with the product information. Both the patients in the intervention arm and the patients in the comparator arm received 4 to 6 cycles of the study medication followed by monotherapy with atezolizumab in

the intervention arm or, at the discretion of the investigator, best supportive care (BSC) or pemetrexed in the comparator arm.

Patients were treated until disease progression, the occurrence of unacceptable toxicity, discontinuation of treatment by the patient, or death. After disease progression, patients were able to receive monotherapy with atezolizumab as follow-up therapy if they were eligible. These patients were censored for the evaluation of adverse events at the time of treatment change.

In the IMpower130 study, overall survival and PFS were defined as co-primary endpoints. The study duration is event-driven and defined up to the point in time when 457 events in the endpoint overall survival occurred in the WT population. There are two data cut-offs. The first data cut-off of 15 March 2018 is the pre-specified analysis after the occurrence of 352 events in the overall survival endpoint. Results for all patient-relevant endpoints are available for this data cut-off. The second non-specified data cut-off of 4 September 2018, was requested by the European Medicines Agency (EMA) and includes only data on overall survival.

For the assessment of overall survival, the data of the 2nd data cut-off of the NEoM population is used; which was requested by the European Medicines Agency (EMA) as part of the approval process. For the endpoints of the morbidity and quality of life categories, the data of the NEoM population from the 1st data cut-off are used. For the endpoints in the side effects category, the pharmaceutical company presents only the results of the WT population. Since the proportion of patients with PD-L1 expression ≥ 50% in the WT population is less than 20%, in the present case constellation, the data of the WT population from the 1st data cut-off are used for the assessment of the additional benefit in the side effects category.

Extent and probability of the additional benefit

Mortality

Overall survival is defined as the time between randomisation and death by any cause.

In the IMpower130 study, the median survival time at the time of the 2nd data cut-off of 4 September 2018 was 13.1 months in the reference arm and 18.2 months in the intervention arm for the assessment-relevant NEoM population (hazard ratio (HR): 0.83; 95% CI [0.66;1.03], p value = 0.096). Overall, the difference is not statistically significant. An additional benefit of atezolizumab in combination with nab-paclitaxel and carboplatin for the endpoint mortality is thus not proven.

Morbidity

Progression-free survival (PFS)

For progression-free survival (PFS), there is a statistically significant difference in favour of atezolizumab in combination with nab-paclitaxel and carboplatin (HR = 0.79; 95% CI [0.64; 0.96], p value = 0.0204). The median PFS was 6.5 months in patients in the comparator arm and 7.1 months in patients in the intervention arm.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was collected as an independent endpoint via the endpoint overall survival. The morbidity component was not surveyed on the basis of symptoms but rather exclusively by means of imaging procedures (according to RECIST 1.1).

Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The extent of the additional benefit remains unaffected because even if the present result on the PFS were taken into account in the overall assessment, the overall statement on the extent of the additional benefit would remain unchanged. This is based on the fact that the data from the IMpower130 study do not show a statistically significant result for the endpoints morbidity and health-related quality of life. Accordingly, prolonged PFS was not associated with an advantage in terms of

morbidity or quality of life. Data on morbidity and health-related quality of life are potentially relevant in this respect, especially when, as in the present case, a radiologically determined disease progression is associated with effects on morbidity and/or quality of life. A statistically significant effect on overall survival was not shown at the time of the 2nd data cut-off of 4 September 2018 of the IMpower130 study, which was relevant for the benefit assessment. Against this background, the present extent of the effect on the PFS is not assessed as sufficient enough to reach a different conclusion on the extent of the additional benefit in the overall assessment.

Symptomatology

In the IMpower130 study, the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires were used to record the symptomatology. In both cases, the time until the 1st clinically relevant deterioration is defined as an increase in score of at least 10 points from baseline.

There are no statistically significant differences between the study arms in either questionnaire.

An additional benefit of atezolizumab in combination with nab-paclitaxel and carboplatin for the endpoint symptomatology is thus not proven.

Health status

In the IMpower130 study, health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the benefit assessment, the pharmaceutical company presents responder analyses for the period up to the 1st clinically relevant deterioration in which a change on the VAS of at least 7 or 10 points compared with baseline was defined as a response. These responder analyses were not used in the IQWiG dossier evaluation because the study underlying the derivation of the minimal important difference (MID) (Pickard *et al.*, 2007) of the IQWiG was classified as unsuitable to validate the MID. This is justified 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. Furthermore, the evaluation of EQ-5D by means of responder analyses was not predefined. Given the fact that the validation study in question has already been used in earlier evaluations, in the present evaluation, the G-BA nevertheless uses the responder analyses to assess the effects on the health status.

The responder analyses based on an MID of 10 points show no statistically significant differences between the study arms. An additional benefit of atezolizumab in combination with nab-paclitaxel and carboplatin for the endpoint health status is thus not proven.

Quality of life

In the IMpower130 study, the functional scales of the questionnaire EORTC QLQ-C30 were used to assess the health-related quality of life. The time until the 1st clinically relevant deterioration is considered; this is defined as a decrease in score by at least 10 points from baseline, whereby there was no statistically significant difference between the treatment arms for this endpoint in the NEoM population.

The sub-group analyses show an effect modification for the characteristic liver metastases at the start of study. There is a statistically significant disadvantage for the endpoints global health status (interaction: p value = 0.017) and cognitive function (interaction: p value = 0.029) in the sub-group of patients with liver metastases at the start of study. In patients without liver metastases at the start of study, there is no statistically significant difference.

In addition, the sub-group analyses for the endpoint social function (interaction: p value = 0.003) revealed an effect modification for the characteristic smoker status. This shows a statistically significant advantage for non-smokers. For former or active smokers, there is no statistically significant difference.

Effect modifications for the characteristics liver metastases at the start of study and smoker status were not shown for any other endpoints in the IMpower130 study. The significance of the subgroup analyses is therefore deemed to be too low overall to assess the additional benefit in the endpoint category quality of life separately according to the characteristic liver metastases at the start of study or smoker status.

Thus, when taking into consideration the NEoM population, there is no additional benefit of atezolizumab in combination with nab-paclitaxel and carboplatin for the endpoint category quality of life.

Side effects

Adverse events (AE)

In the IMpower130 study, a survey of AE up to 30 days after the end of treatment or the start of a new antineoplastic therapy was planned. Adverse events occurred at least once in almost every patient in both treatment arms. The results for the AE endpoint are therefore presented only on a supplementary basis.

Serious adverse events (SAE), immune mediated AE, immune mediated SAE, immune mediated severe AE (CTCAE grade 3–4)

In the IMpower130 study, the survey of SAE, immune mediated AE, immune mediated SAE, and immune mediated severe AE (CTCAE grade 3–4) was planned up to 90 days after the end of treatment or when a new antineoplastic therapy was started. No information is available on the time period between therapy discontinuation and start of follow-up therapy. For the present therapeutic indication, it can be assumed that the start of a follow-up therapy is not immediate but rather takes place within a narrow time window after therapy discontinuation. Thus, if patients are censored at the time of the change of therapy, information on a not insignificant observation period is missing for these endpoints; this means that a relevant proportion of events may not be considered.

For SAE, immune mediated AE, immune mediated SAE, and immune mediated severe AE (CTCAE grade 3–4), there are thus no usable data.

In the view of the G-BA, the chosen operationalisation is problematic for the assessment, and the present result of this operationalisation could have been avoided by setting a uniform duration for the follow-up.

Severe AE (CTCAE grade 3–4)

In the IMpower130 study, events for the severe AE endpoint were followed up for 30 days. Also for this endpoint, censoring at the time of the start of follow-up therapy may result in a shorter follow-up period. However, because the maximum follow-up period is 30 days, it is assumed that this has no relevant impact on the outcome for this endpoint.

For the endpoint severe AE (CTCAE grade 3–4), there is a statistically significant difference to the disadvantage of atezolizumab in combination with nab-paclitaxel and carboplatin compared with nab-paclitaxel and carboplatin (HR: 1.24; 95% CI [1.03;1.49]; p = 0.026).

Discontinuation because of AE

For the endpoint “Discontinuation because of AE”, there is no statistically significant difference between the treatment arms.

Specific AE (severe AE with CTCAE grade 3–4)

For specific AE, only specific AE for severe AE with CTCAE grade 3–4 were selected. The follow-up was for 30 days. In analogy to the end point severe AE, a shorter follow-up period because of the censoring of therapy changers is also not considered relevant for the specific AE (severe AE with CTCAE grade 3–4).

For blood and lymphatic system disorders (SOC) as well as examinations (SOC), syncope (PT) and dyspnoea (PT), there is a statistically significant difference to the disadvantage of atezolizumab in combination with platinum-based chemotherapy compared with platinum-based chemotherapy.

Overall assessment

To assess the additional benefit of atezolizumab in combination with platinum-based chemotherapy, the open-label, randomised IMpower130 Phase III study is used to compare atezolizumab in combination with nab-paclitaxel and carboplatin with nab-paclitaxel and carboplatin. Results on mortality (overall survival), morbidity, health-related quality of life, and side effects are available for this study.

For overall survival, an additional benefit for treatment with atezolizumab in combination with nab-paclitaxel and carboplatin is not proven because there is no statistically significant difference between the treatment arms.

Regarding the health status, measured by EQ-5D VAS, and the symptomatology, measured by EORTC QLQ-C30 and EORTC QLQ-LC13, there are no statistically significant differences between the study arms.

Similarly, based on the NEoM population using the functional scales of the EORTC QLQ-C30, there is no statistically significant differences between the treatment arms for the endpoint category quality of life.

With regard to side effects, no usable statements are available for the endpoints serious adverse events (SAE) and for specific adverse events of immune mediated side effects. For the severe AE (CTCAE grade 3–4) as well as a selection of specific severe AE (CTCAE grade 3–4), there is a disadvantage for atezolizumab in combination with nab-paclitaxel and carboplatin. For the endpoint “Discontinuation because of AE”, there is no statistically significant difference between the treatment arms.

In the overall view, there are no statistically significant differences for the endpoint categories overall survival, morbidity, and quality of life. The disadvantages for atezolizumab in combination with nab-paclitaxel and carboplatin for severe AE (CTCAE grade 3–4) are considered significant for patients. However, considering the rate of treatment discontinuation, which does not differ statistically significantly between treatment groups, the overall disadvantages in terms of side effects are not considered as serious as to justify the determination of a lesser benefit in the overall assessment.

In summary, in the overall assessment of the results on mortality, morbidity, quality of life, and side effects, an additional benefit of atezolizumab in combination with nab-paclitaxel and carboplatin compared with nab-paclitaxel and carboplatin for the first-line treatment of metastatic non-squamous NSCLC without EGFR- or ALK-positive tumour mutations in patients with a PD-L1 expression of < 50% (TPS) is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient atezolizumab in combination with nab-paclitaxel and carboplatin. Atezolizumab, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC.

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

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

b) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

About patient group a)

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

- Pembrolizumab as monotherapy

For this patient population, the pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of atezolizumab compared with the appropriate comparator therapy.

In the overall view, an additional benefit of atezolizumab in combination with nab-paclitaxel and carboplatin is therefore not proven for the present patient population.

About patient group b)

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

- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)

or

- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed; *cf* Annex VI to Section K of the Pharmaceuticals Directive)

or

- Carboplatin in combination with nab-paclitaxel

or

- Pembrolizumab in combination with pemetrexed and platinum chemotherapy

For this patient group, data from the open-label, randomised IMpower130 Phase III study are considered. These allow comparative statements on atezolizumab in combination with nab-paclitaxel and carboplatin compared with nab-paclitaxel and carboplatin for the endpoint categories overall survival (mortality), morbidity, quality of life, and side effects.

For the endpoint categories mortality (overall survival), morbidity, and quality of life, no statistically significant differences in the assessment-relevant NEoM sub-population wereobserved between the study arms.

For the endpoint category side effects, there are statistically significant disadvantages for the atezolizumab combination therapy in severe AE (CTCAE grade 3–4) and other specific AE.

In the overall view, there are no statistically significant differences for the endpoint categories overall survival, morbidity, and quality of life. The disadvantages for atezolizumab in combination with nab-paclitaxel and carboplatin for severe AE (CTCAE grade 3–4) are considered significant for patients. However, considering the rate of treatment discontinuation, which does not differ statistically significantly between treatment groups, the overall disadvantages in terms of side effects are not considered as serious as to justify the determination of a lesser benefit in the overall assessment.

In conclusion, there is no additional benefit of atezolizumab in combination with nab-paclitaxel and carboplatin compared to nab-paclitaxel and carboplatin.

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

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

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

For the number of German patients with lung cancer, the incidence for 2019 (56,979) patients from the previous resolution on pembrolizumab (resolution of 19 September 2019) is used for the calculations. This patient group is limited to the target population via 9 calculation steps:

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

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

8b. The proportion of patients with Stage IV NSCLC with PD-L1 expressing tumours (TPS < 50%) is 71.1%.[3]

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

For

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

approx. 2,320 to 2,640 patients

b) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

approx. 5,700 to 6,480 patients

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

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Tecentriq® (active ingredient: atezolizumab) at the following publicly accessible link (last access: 11 February 2020):

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

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

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

- Training material for health professionals
- Patient pass

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2020).

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

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

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

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

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

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Induction therapy				
Atezolizumab	1 × per 21-day cycle	4–6 cycles	1	4–6
+ carboplatin	1 × per 21-day cycle	4–6 cycles	1	4–6
+ nab-paclitaxel	3 × per 21-day cycle	4–6 cycles	3	12–18
Maintenance treatment				
Atezolizumab	1 × per 21-day cycle	11.4–13.4 cycles	1	11.4–13.4
Appropriate comparator therapy				
a) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy				
Pembrolizumab	1 × per 21-day cycle	17.4 cycles	1	17.4
b) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy				
Cisplatin or carboplatin in combination with a third generation cytostatic agent				
Cisplatin	1 × per 21-day cycle	17.4 cycles	1	17.4

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Carboplatin	1 × per 21-day cycle	17.4 cycles	1	17.4
+ docetaxel	1 × per 21-day cycle	17.4 cycles	1	17.4
+ gemcitabine	2 × per 21-day cycle	17.4 cycles	2	34.8
+ paclitaxel	1 × per 21-day cycle	17.4 cycles	1	17.4
+ pemetrexed	1 × per 21-day cycle	17.4 cycles	1	17.4

(Continuation)

+ vinorelbine	2 × per 21-day cycle	17.4 cycles	2	34.8
Carboplatin in combination with nab-paclitaxel				
Carboplatin	1 × per 21-day cycle	17.4 cycles	1	17.4
+ nab-paclitaxel	3 × per 21-day cycle	17.4 cycles	3	52.2

Usage and consumption:

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

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Induction therapy					
Atezolizumab	1200 mg	1200 mg	1 × 1200 mg	4–6	4 × 1200 mg

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

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
					– 6 × 1200 mg
+ carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg +1 x 450 mg	4–6	4 × 600 mg + 4 × 450 mg – 6 × 600 mg + 6 × 450 mg
+ nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 × 100 mg	12–18	24 × 100 mg – 36 × 100 mg
Maintenance treatment					
Atezolizumab	1200 mg	1200 mg	1 × 1200 mg	11.4 – 13.4	11.4 × 1200 mg – 13.4 × 1200 mg

(Continuation)

Appropriate comparator therapy					
a) <u>Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy</u>					
Pembro-lizumab	200 mg	200 mg	2 × 100 mg	17.4	34.8 × 100 mg
b) <u>Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy</u>					
Cisplatin or carboplatin in combination with a third generation cytostatic agent					
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 × 100 mg + 1 × 50 mg	17.4	17.4 × 100 mg + 17.4 × 50 mg
	80 mg/m² = 152 mg	152 mg	1 × 100 mg + 1 × 50 mg + 1 × 10 mg	17.4	17.4 × 100 mg + 17.4 × 50 mg + 17.4 × 10 mg
	100 mg/m² = 190 mg	190 mg	2 × 100 mg	17.4	34.8 × 100 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg +1 x 450 mg	17.4	17.4 × 600 mg + 17.4 × 450 mg
+ docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 × 160 mg	17.4	17.4 × 160 mg
+ gemcitabine	1250 mg/m² = 2375 mg	2375 mg	1 × 2,000 mg + 2 × 200 mg	34.8	34.8 × 2,000 mg + 69.6 × 200 mg

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
+ paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	1 × 150 mg + 2 × 100 mg	17.4	17.4 × 150 mg + 34.8 × 100 mg
+ pemetrexed	500 mg/m² = 950 mg	950 mg	2 × 500 mg	17.4	34.8 × 500 mg
+ vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 × 50 mg	34.8	34.8 × 50 mg
	30 mg/m² = 57 mg	57 mg	1 × 50 mg + 1 × 10 mg	34.8	34.8 × 50 mg + 34.8 × 10 mg

(Continuation)

Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg +1 x 450 mg	17.4	17.4 × 600 mg + 17.4 × 450 mg
+ nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 × 100 mg	52.2	104.4 × 100 mg

Costs:

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 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.

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Induction therapy					
Atezolizumab	1 CIS	€ 4,692.05	€ 1.77	€ 264.69	€ 4,425.59
Carboplatin 450 mg	1 CIS	€ 227.97	€ 1.77	€ 10.29	€ 215.91

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
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Nab-paclitaxel	1 PIS	€ 429.09	€ 1.77	€ 52.91	€ 374.41
Maintenance treatment					
Atezolizumab	1 CIS	€ 4,692.05	€ 1.77	€ 264.69	€ 4,425.59

(Continuation)

Appropriate comparator therapy					
a) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy					
Pembrolizumab	1 CIS	€ 3,083.93	€ 1.77	€ 172.85	€ 2,909.31
b) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy					
Cisplatin or carboplatin in combination with a third generation cytostatic agent					
Cisplatin 10 mg	1 CIS	€ 17.26	€ 1.77	€ 0.30	€ 15.19
Cisplatin 50 mg	1 CIS	€ 47.43	€ 1.77	€ 1.73	€ 43.93
Cisplatin 100 mg	1 CIS	€ 76.31	€ 1.77	€ 3.10	€ 71.44
Carboplatin 450 mg	1 CIS	€ 227.97	€ 1.77	€ 10.29	€ 215.91
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Docetaxel	1 CIS	€ 1,397.36	€ 1.77	€ 175.44	€ 1,220.15
Gemcitabine 200 mg	1 CIS	€ 28.57	€ 1.77	€ 0.83	€ 25.97
Gemcitabine 2000 mg	1 CIS	€ 193.96	€ 1.77	€ 8.68	€ 183.51
Paclitaxel 100 mg	1 CIS	€ 360.27	€ 1.77	€ 16.57	€ 341.93

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Paclitaxel 150 mg	1 CIS	€ 535.31	€ 1.77	€ 24.88	€ 508.66
Pemetrexed 500 mg	1 PIK	€ 2,533.30	€ 1.77	€ 558.64	€ 1,972.89
Vinorebline 10 mg	10 CIS	€ 293.74	€ 1.77	€ 13.42	€ 278.55
Vinorelbine 50 mg	10 CIS	€ 1,424.29	€ 1.77	€ 67.07	€ 1,355.45

(Continuation)

Carboplatin in combination with nab-paclitaxel					
Carboplatin 450 mg	1 CIS	€ 227.97	€ 1.77	€ 10.29	€ 215.91
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Nab-paclitaxel	1 PIS	€ 429.09	€ 1.77	€ 52.91	€ 374.41

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

Costs for additionally required SHI services:

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

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

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

Designation of the therapy	Package size	Costs (pharmacy selling price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/year	Costs/patient/year
Appropriate comparator therapy							
Cisplatin							
Anti-emetic treatment							
In clinical practice, appropriate anti-emetic treatment is established before and/or after cisplatin administration. The product information of cisplatin does not contain any concrete information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% infusion solution, 37.5 g/day	10 × 500 ml IS	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
Sodium chloride 0.9% infusion solution, 3–4.4 l/day	10 × 1,000 ml IS	€ 35.47	€ 1.77	€ 1.12	€ 32.58	17.4	€ 170.07 -
	10 × 500 ml IS	€ 22.72	€ 1.14	€ 0.69	€ 20.89		€ 263.11
Paclitaxel							
Dexamethasone 20 mg[9]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84	17.4	€ 81.32
Dimetindene i.v. 1 mg/10 kg	5 × 4 mg SFI	€ 18.62	€ 1.77	€ 1.97	€ 14.88	17.4	€ 103.56
Ranitidine 50 mg i.v.	5 CIS	€ 15.08	€ 1.77	€ 0.19	€ 13.12	17.4	€ 45.66
Pemetrexed							
Dexamethasone[9] 2 × 4 mg	100 TAB 4 mg	€ 79.27	€ 1.77	€ 5.40	€ 72.10	52.2	€ 75.27
Folic acid: 350–1,000 µg/day[10]	100 × 400 µg TAB	€ 15.96	€ 0.80	€ 2.34	€ 12.82	365	€ 46.79 – 93.59
Vitamin B12[10] *1,000 µg/day*	10 × 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.33	€ 6.70	6	€ 4.02
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; IS: infusion solution; TAB = tablets							

[9] Fixed reimbursement rate

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

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

By letter dated 26 September 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient atezolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 20 December 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 January 2020. The deadline for submitting written statements was 23 January 2020.

The oral hearing was held on 10 February 2020.

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

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

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

The patient representatives support the resolution.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	12 February 2019	Determination of the appropriate comparator therapy
Working group Section 35a	5 February 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	10 February 2020	Conduct of the oral hearing
Working group Section 35a	19 February 2020 4 March 2020 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