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: Breast Cancer

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 26 August 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 19 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 (mammary carcinoma) 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, 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 nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease

A systemic therapy containing anthracycline and/or taxane, taking into account the marketing authorisation of the medicinal products.

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. The chemotherapeutic agents cyclophosphamide, docetaxel, doxorubicin, doxorubicin (liposomal), epirubicin, eribulin, 5-fluorouracil, gemcitabine, ifosfamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, vincristine, and vinorelbine as well as the antibody bevacizumab have a marketing authorisation for the present therapeutic indication.

On 2. In principle, radiotherapy can be considered as a non-medicinal treatment.

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

- Annex VI to Section K of the Pharmaceuticals Directive – Active ingredients that are not prescribable in off-label use (last revised: 17 October 2019): Gemcitabine in monotherapy for female breast cancer

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.

Because the therapeutic indication refers to triple-negative receptor status, endocrine therapies and therapies indicated exclusively for HER2-positive breast cancer will not be considered.

The evidence for therapeutic options in the therapeutic indication only partly explicitly refers to the patient population with proven triple-negative breast cancer. Even in the therapy recommendations of the guidelines, the characteristic “triple-negative breast cancer” is predominantly not explicitly addressed. However, a corresponding differentiation results from the distinct recommendations for patients with HER2-positive or hormone receptor-positive breast cancer.

Accordingly, cytotoxic chemotherapy represents the standard of care in the first-line treatment of metastatic or unresectable locally advanced triple-negative breast cancer. Based on recommendations in the guidelines, the chemotherapy should contain an anthracycline or a taxane. Monochemotherapy with an anthracycline or a taxane as well as combination therapy is an established treatment option. Taking into account the respective marketing authorisations, the monotherapies doxorubicin, doxorubicin (liposomal), epirubicin, and docetaxel as well as paclitaxel are therefore considered.

Combination therapy mainly consists of the combination of different chemotherapies, including an anthracycline or a taxane or a combination of both. In according with the evidence and marketing authorisation, eligible combination therapies include paclitaxel in combination with an anthracycline (epirubicin + paclitaxel) as well as in combination with gemcitabine, docetaxel in combination with doxorubicin as well as in combination with capecitabine, doxorubicin (also liposomal) + cyclophosphamide, epirubicin + cyclophosphamide, epirubicin + docetaxel, and epirubicin + paclitaxel.

Combination chemotherapy has stronger effects but is also associated with more severe side effects. It may, for example, be indicated in cases of rapid tumour growth or severe symptoms. In addition to other chemotherapies, the combination with the VEGF

antibody bevacizumab can also be considered. Based on the evidence available, bevacizumab is a possible, but not a regular, therapy option.

A non-medicinal therapy (radiotherapy) is not an appropriate comparator therapy in the present therapy situation.

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 is assessed as follows:

For atezolizumab in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease, there is a hint for a non-quantifiable additional benefit.

Justification:

The pharmaceutical company has presented the results of the IMpassion 130 study to prove the additional benefit. The IMpassion 130 study is a randomised, double-blind, controlled study comparing atezolizumab + nab-paclitaxel with nab-paclitaxel. The treatment was performed in 28-day cycles. In the test arm, atezolizumab (840 mg) was applied on Day 1 and Day 15; in both the test and comparator arm, nab-paclitaxel was applied on Days 1, 8, and 15 at a dosage 100 mg/m² BSA. In both arms, the treatment was to be performed for at least 6 cycles.

A total of 902 patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy or targeted systemic therapy for this stage were enrolled in the study. They were stratified according to previous taxane therapy (yes vs no), the presence of liver metastases (yes vs no), and PD-L1 status (PD-L1 status of tumour infiltrating immune cells ≥ 1%: yes vs no) and randomised to the two study arms at a ratio of 1:1.

In the dossier, the sub-population of patients whose tumours show a PD-L1 expression ≥ 1% of tumour-infiltrating immune cells was presented according to the approved therapeutic indication. 185 patients in the test arm and 184 patients in the reference arm corresponded to this sub-population. In terms of demographic and clinical characteristics, the two study arms were balanced even after the sub-population was formed.

51.9% of patients in the test arm and 52.7% of patients in the control arm had previously received taxane-based therapy in the neoadjuvancy‡ or adjuvancy‡. Prior neoadjuvant or adjuvant anthracycline-based therapy was given to 58.9% of patients in the test arm and 54.9% in the control arm. The period between the end of neoadjuvant or adjuvant therapy and randomisation into the study had to be at least 12 months.

For the endpoint categories, results for different data cut-offs were presented in the dossier. The evaluations of mortality are based on the data cut-off of 2 January 2019. Because no patient in the comparator arm and only 10% of the patients in the intervention arm were under treatment for this data cut-off but side effects were surveyed only 30 days after treatment, the previous data cut-off of 3 September 2018, which was collected for the FDA, is used for the side effects category. For the patient-reported outcomes in the categories morbidity and quality of life, results of the pre-specified data cut-off of 17 April 2018 were presented.

Implementation of the appropriate comparator therapy:

The determination of the appropriate comparator therapy (anthracycline- and/or taxane-containing systemic therapy) indicates that the marketing authorisation of the medicinal products should be taken into account. The active ingredient nab-paclitaxel from the taxane

class is not approved for first-line treatment of locally advanced or metastatic breast cancer. In order to prove that nab-paclitaxel is sufficiently comparable in therapeutic benefit to a taxane approved for the present therapeutic indication, the pharmaceutical company has presented data from various clinical studies in the dossier. These are on the one hand the studies of Luhn (2019; Flatiron Health database), Gradishar (2005; Study CA0120-0), and Rugo (2015). Furthermore, the studies of Gianni (2018), Untch (2016), Schneeweiß (2018), Gradishar (2009), and Gradishar (2012) as well as the meta-analysis of Miles (2013) were presented.

Of these studies, the G-BA considers the publications of Gradishar (2009) and Gradishar (2012) to be particularly suitable. These are based on a Phase II study in which patients with previously untreated metastatic breast cancer were randomised to the following study arms: 1. nab-paclitaxel 300mg/m² body surface (BSA) every three weeks, 2. nab-paclitaxel 100mg/m² BSA every week, 3. nab-paclitaxel 150mg/m² BSA every week, and 4. docetaxel 100mg/m² BSA every three weeks. Results on treatment response (progression-free survival and overall response rate) can be found in Gradishar (2009). Data on overall survival were not yet available at that time; these were presented within the 2012 publication.

Although the statistical significance of this Phase II study is limited and the authors also point out that the results should be confirmed in a Phase III study, the G-BA considers the study to be sufficiently suitable in terms of best available evidence in order to be able to assess the comparability of the therapeutic benefit of nab-paclitaxel with a taxane (in this case docetaxel), which is approved for the present therapeutic indication of atezolizumab. This evaluation is made with regard to the question as to whether the IMpassion 130 study with nab-paclitaxel is suitable as a comparator for assessing the additional benefit of atezolizumab + nab-paclitaxel.

In addition, the written statements of clinical experts in the present procedure on this issue will be used for this evaluation. Overall, these indicate the relevance of nab-paclitaxel in the present therapy situation. This is also reflected in current guidelines, including the German S3 guideline of the AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) in which nab-paclitaxel is either explicitly recommended or included in a recommendation for taxane therapy.

The G-BA concludes that the IMpassion 130 study with nab-paclitaxel as a comparator is sufficiently suitable to assess the additional benefit of atezolizumab + nab-paclitaxel. However, in view of the available alternatives, the G-BA views the selection of nab-paclitaxel as a comparator for the IMpassion 130 study critically and limits the scientific knowledge gained from this study. On the basis of the objections raised and information provided in the statement procedure, it can be concluded that treatment with nab-paclitaxel only partially reflects the reality of care in Germany. Furthermore, there are uncertainties regarding the dosage of 100 mg/m² weekly nab-paclitaxel regularly used in the IMpassion 130 study.

With regard to the dosage of nab-paclitaxel, guidelines mainly refer to a dosage of 125 mg/m² BSA weekly on days 1, 8, and 15 of a 28-day cycle. The dosage of 100 mg/m² used in the IMpassion130 study was also critically discussed in the statements of clinical experts. However, with regard to toxicities and associated therapy discontinuations, a reduced dosage of 100 mg/m² could also be acceptable. However, the majority of patients enrolled in the present study were in good general condition according to ECOG-Performance Status at the start of study.

The G-BA considers the special therapy and care situation in the present therapeutic indication and the corresponding statements by medical experts in the present procedure to be a sufficient medical reason that justifies the use of nab-paclitaxel as a sufficiently suitable comparator for the benefit assessment despite remaining relevant uncertainties.

The G-BA points out that it will continue to adhere to the principles laid down in the provisions on benefit assessment according to Section 35a SGB V (Ordinance on the Benefit Assessment of Pharmaceuticals and Chapter 5 of the Rules of Procedure of the Federal Joint Committee), and thus also to the requirement laid down in Chapter 5, Section 6, paragraph 3, sentence 2, No. 1 VerfO that the comparator therapy is used in the clinical trial used for benefit assessment in compliance with the marketing authorisation.

If the nab-paclitaxel used as comparator in this study has been used in a manner that is not compliant with marketing authorisation, it is not possible to draw any conclusions about its usefulness in the application form that exceeds the authorisation in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V.

Extent and probability of the additional benefit

Mortality

For the endpoint overall survival, there is a statistically significant difference in favour of atezolizumab + nab-paclitaxel (hazard ratio (HR): 0.71; [95% confidence interval (CI): 0.54; 0.93]; p value 0.013). Median overall survival in the test arm is prolonged by 7 months compared with the reference arm (25.0 vs 18.0 months).

The study thus shows a clearly positive effect of atezolizumab + nab-paclitaxel compared with nab-paclitaxel.

Morbidity

Progression-free survival (PFS)

Progression-free survival assessed by the investigator (INV-PFS) is a co-primary endpoint of the IMpassion130 study. The PFS is operationalised as the time between randomisation and time of onset of disease progression assessed by the investigator and based on the RECIST v1.1 criteria or occurrence of death by any cause.

Therapy with atezolizumab + nab-paclitaxel shows a significantly longer progression-free survival compared with nab-paclitaxel (7.5 vs 5.3 months; HR: 0.63; [95% CI: 0.50; 0.080]; p value < 0.0001).

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 using imaging procedures (radiologically determined disease progression according to the RECIST v1.1 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 IMpassion130 study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module QLQ-BR23.

The survey of symptomatology was operationalised as the time to first deterioration (increase) by 10 points on the respective symptom scale.

Analyses of the data cut-off of 17 April 2018 were presented.

Within the symptom scales of EORTC QLQ-C30, there is a statistically significant disadvantage to the detriment of atezolizumab + nab-paclitaxel for the pain scale. In the fatigue, nausea and vomiting, dyspnoea, insomnia, loss of appetite, constipation, and diarrhoea scales, there are no statistically significant differences.

In the scales “side effects of the therapy”, “symptoms in the breast area” and “symptoms in the arm area” of the BR23 symptom scales, there is also no significant difference between the treatment arms. For the scale “burden of hair loss”, there is no usable data.

Overall, under treatment with atezolizumab + nab-paclitaxel, there is a disadvantage for symptomatology; this is due to the pain endpoint.

Health status

In the IMpassion 130 study, health status was assessed using the visual analogue scale of EQ-5D. The survey was operationalised as the time to first deterioration by 10 points.

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 event time analyses, there was no statistically significant difference between the two treatment arms.

There is therefore no advantage or disadvantage in terms of health status.

Quality of life

In the IMpassion130 study, the symptomatology was measured using the functional scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module QLQ-BR23.

The survey of quality of life was operationalised as the time to first deterioration (decrease) by 10 points on the respective symptom scale.

In none of the function scales of EORTC QLQ-C30 ("global health status", "role function", "physical function" "emotional function", "cognitive function" and "social function") is there a statistically significant difference between the treatment arms.

There are also no statistically significant differences for the functional scales "body image", "future perspective", and "sexual activity" of the additional module QLQ-BR23. For the scale "sexual pleasure", there is no usable data.

In terms of quality of life, no advantage or disadvantage of atezolizumab + nab-paclitaxel can be identified.

Side effects

Adverse events (AE in total)

The results for the "combined adverse events" endpoint are presented only on a supplementary basis.

In the test arm, 100% and 97.8% of patients in the comparator arm experienced an adverse event at least once.

Serious adverse events (SAE)

In terms of SAE, there is no statistically significant difference between the two treatment arms (HR: 1.17; [95% CI: 0.74; 1.87]; p = 0.501).

Severe adverse events (CTCAE grade 3–4)

There is no statistically significant difference with regard to severe adverse events (CTCAE grade 3–4) (HR: 1.20; [95% CI: 0.89; 1.63]; p = 0.234).

Discontinuation because of AE

With regard to discontinuation because of AE, there is a statistically significant disadvantage to the detriment of atezolizumab + nab-paclitaxel (HR: 2.34; [95% CI: 1.24; 4.41]; p = 0.007). In the test arm, 37% of patients discontinued therapy because a AE; in the comparator arm, only 7.2% of patients did.

Specific AE

Immune mediated AE

With regard to the endpoint immune mediated AE, there is a statistically significant difference to the disadvantage of atezolizumab + nab-paclitaxel (HR: 1.63; [95% CI: 1.20; 2.22]; p = 0.002). The event rate was 57.8% in the test arm and 36.5% in the control arm.

Immune mediated SAE

Regarding immune mediated SAE, there is no statistically significant difference between the two study arms (HR: 0.80; [95% CI: 0.16; 3.96]; p = 0.778).

Immune mediated severe AE (CTCAE grade 3–4)

For the endpoint immune mediated severe AE (CTCAE grade 3–4), there is no statistically significant difference (HR: 1.20; [95% CI: 0.46; 3.17]; p = 0.710).

Other specific AE

Investigations (system organ class [SOC], severe AE, CTCAE grade 3–4)

With regard to the endpoint, there is a statistically significant difference to the detriment of atezolizumab + nab-paclitaxel (HR: 2.06; [95% CI: 1.02; 4.18]; p = 0.041).

Overall, for the side effects category, there are disadvantages in individual endpoints for atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel. These are shown for the endpoint "discontinuation because of AE" and, when considered in detail, for the endpoints "immune mediated AE" and "examinations (SOC, severe AE, CTCAE grade 3–4)".

Overall assessment

For the assessment of the additional benefit of atezolizumab in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease, data on mortality, morbidity, quality of life, and side effects from the IMpassion130 study are available.

The comparator nab-paclitaxel is not approved for this therapeutic indication. However, the G-BA came to the conclusion that the IMpassion 130 study with nab-paclitaxel as a comparator is sufficiently suitable to assess the additional benefit of atezolizumab + nab-paclitaxel. In view of the available alternatives, the G-BA views the selection of nab-paclitaxel as a comparator for the IMpassion 130 study critically and limits the scientific knowledge gained from this study. On the basis of the objections raised and information provided in the statement procedure, it can be concluded that treatment with nab-paclitaxel only partially reflects the reality of care in Germany. Furthermore, there are uncertainties regarding the dosage of 100 mg/m² weekly nab-paclitaxel regularly used in the IMpassion 130 study.

With regard to the dosage of nab-paclitaxel, guidelines mainly refer to a dosage of 125 mg/m² BSA weekly on days 1, 8, and 15 of a 28-day cycle. The dosage of 100 mg/m² used in the IMpassion130 study was also critically discussed in the statements of clinical experts. However, with regard to toxicities and associated therapy discontinuations, a reduced dosage of 100 mg/m² could also be acceptable. However, the majority of patients enrolled in the present study were in good general condition according to ECOG-Performance Status at the start of study. Nevertheless, relevant uncertainties must be taken into account. In view of the available alternatives, the G-BA views the selection of nab-paclitaxel as a comparator for the IMpassion 130 study critically.

For overall survival, the IMpassion130 study showed a statistically significant, clearly positive effect for atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel.

In the morbidity category, there is a statistically significant disadvantage in favour of atezolizumab + nab-paclitaxel for the endpoint "pain". There are no differences between the study arms in the other symptom scales or in health status.

In terms of quality of life there is no advantage or disadvantage for atezolizumab + nab-paclitaxel.

In the side effects category, there are disadvantages with regard to discontinuation because of AE and, in detail, specific AE under atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel.

Overall, the advantage in overall survival is offset by disadvantages in endpoints in the morbidity and side effects categories. These disadvantages are considered relevant but do not call into question the positive effect on overall survival. Because of the uncertainties regarding the comparator nab-paclitaxel, the extent of the additional benefit determined on the basis of the results of the IMPassion 130 study cannot be quantified.

Thus for atezolizumab in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose

tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease, a non-quantifiable additional benefit was determined.

Reliability of data (probability of additional benefit)

The underlying IMpassion 130 study is a randomised, controlled, double-blind study.

The risk of bias at the study level is classified as low.

With regard to the endpoints overall survival and discontinuation because of AE, the risk of bias is classified as low. For the endpoints of the symptomatology and health-related quality of life categories, the risk of bias is estimated to be high because of a high proportion of patients not included in the analysis.

In addition, with respect to the nab-paclitaxel comparator and its dosage in the IMpassion 130 study, there are still uncertainties with regard to the reliability of data of the established additional benefit.

As a result, taken as a whole, the reliability of data of an additional benefit is considered as a hint.

2.1.4 Summary of the assessment

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

The therapeutic indication assessed here is as follows:

Atezolizumab in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

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

A systemic therapy containing anthracycline and/or taxane, taking into account the marketing authorisation of the medicinal products.

The pharmaceutical company has presented results of the IMpassion 130 study to prove the additional benefit. In this study atezolizumab in combination with nab-paclitaxel is compared with a monotherapy with nab-paclitaxel.

nab-paclitaxel is not approved in the therapy situation to be assessed. In order to prove a sufficiently comparable therapeutic benefit of nab-paclitaxel compared with a taxane approved for the present therapeutic indication, the pharmaceutical company has presented data from various clinical studies in the dossier.

Against the background of the special therapy and care situation in the present therapeutic indication and under consideration of the corresponding statements of medical experts in the present procedure, nab-paclitaxel is considered as a sufficiently suitable comparator for the benefit assessment.

From this, no conclusions can be drawn about the usefulness of nab-paclitaxel in the form of application beyond the scope of authorisation in the standard care of insured persons in the SHI system.

With regard to mortality, there was a statistically significant, clearly positive effect for atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel.

In the morbidity category, there is a statistically significant disadvantage for atezolizumab + nab-paclitaxel for the endpoint “pain”. There are neither advantages nor disadvantages from the other endpoints on symptomatology and health status.

No statistically significant differences are found in the quality of life category.

Within the side effects category, there are isolated disadvantages for atezolizumab + nab-paclitaxel regarding the endpoint “discontinuation because of AE” and in detail in the area of specific AE.

However, the disadvantages do not call into question the positive effect on overall survival. Because of remaining relevant uncertainties regarding the comparator nab-paclitaxel used in the IMpassion130 study, the extent of the additional benefit identified cannot be quantified.

In the overall view, there is a hint for a non-quantifiable additional benefit.

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. However, an overall underestimation must be assumed. On one hand, this is based on a lack of consideration of patients with initial diagnosis in or progression to Stage IIIC before 2019. Furthermore, an underestimation of the upper limit must be assumed because unit value for the initial diagnosis in Stages IIIC to IV may have been too low. There are uncertainties with regard to the unit value for TNBC (lower limit) and the unit value for the PD-L1 expression ≥ 1%.

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/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 gynaecology and obstetrics, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with breast 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).

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 the therapy regime doxorubicin + cyclophosphamide, doxorubicin + docetaxel, epirubicin + cyclophosphamide, epirubicin + docetaxel, and epirubicin + paclitaxel, the treatment modes of the German S3 guideline (version 4.3) were used.[2]

For doxorubicin and epirubicin, the cumulative total dose was considered (450–550 mg/m² for doxorubicin and 900–1,000 mg/m² for epirubicin, respectively). For doxorubicin and epirubicin there is product information with different dosage recommendations (doxorubicin: 50–80 mg/m² and 60–75 mg/m²; epirubicin: 75–90 mg/m² and 60–90 mg/m². The dosage recommendations with the largest range were used for the cost calculation: doxorubicin 50–80 mg/m² and epirubicin: 60–90 mg/m².

For dosages depending on body weight (BW) or body surface, the average body measurements of adult woman were used as a basis (average body size: 1.66 m, average body weight: 68.7 kg).[3] From this, a body surface area of 1.76 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				
Atezolizumab	On Day 1 and 15 of a 28-day cycle	13	2	26
nab-paclitaxel	On Day 1, 8, and 15 of a 28-day cycle	13	3	39
Appropriate comparator therapy: a therapy containing anthracycline and/or taxane				
Docetaxel				
Docetaxel	1 × every 21 days	17.4	1	17.4
Docetaxel + capecitabine				
Docetaxel	1 × every 21 days	17.4	1	17.4
Capecitabine	2 × daily on day 1–	17.4	14	243.6

[2] Guidelines Programme for Oncology (Eds.): Interdisciplinary S3 guideline for the diagnosis, therapy, and after-care of breast cancer, 2018. https://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/

[3] Federal health reporting. Average body measurements of the population (2017), www.gbe-bund.de

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	14 of a 21-day cycle			
Doxorubicin				
Doxorubicin	1 × every 21 days	5–11[4]	1	5–11
Doxorubicin + docetaxel				
Doxorubicin	1 × every 21 days	9–11[4]	1	9–11
Docetaxel	1 × every 21 days	17.4	1	17.4
Doxorubicin + cyclophosphamide				
Doxorubicin	1 × every 21 days	7–9[4]	1	7–9
Cyclophosphamide	1 × every 21 days	17.4	1	17.4
Doxorubicin + paclitaxel				
Doxorubicin	1 × every 21 days	9–11[4]	1	9–11
Paclitaxel	1 × every 21 days	17.4	1	17.4
Doxorubicin (pegylated, liposomal)				
Doxorubicin (pegylated, liposomal)	1 × every 28 days	13	1	13
Liposomal doxorubicin + cyclophosphamide				
Liposomal doxorubicin	1 × every 21 days	17.4	1	17.4
Cyclophosphamide	1 × every 21 days	17.4	1	17.4
Epirubicin				

[4] Based on the total cumulative dose of maximum 450–550 mg/m².

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Epirubicin	1 × every 21 days	10–16[5]	1	10–16
Epirubicin + cyclophosphamide				
Epirubicin	1 × every 21 days	12–16[5]	1	12–16
Cyclophosphamide	1 × every 21 days	17.4	1	17.4
Epirubicin + docetaxel				
Epirubicin	1 × every 21 days	12–13[5]	1	12–13
Docetaxel	1 × every 21 days	17.4	1	17.4
Epirubicin + paclitaxel				
Epirubicin	1 × every 21 days	15–16[5]	1	15–16
Paclitaxel	1 × every 21 days	17.4	1	17.4
Paclitaxel				
Paclitaxel	1 × every 21 days	17.4	1	17.4
Gemcitabine + paclitaxel				
Gemcitabine	On Day 1 and 8 of a 21-day cycle	17.4	2	34.8
Paclitaxel	On Day 1 of a 21-day cycle	17.4	1	17.4

Usage and consumption:

[5] Based on the total cumulative dose of maximum 900–1,000 mg/m².

Designation of the therapy	Dosage/ use	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Atezolizumab	840 mg	840 mg	1 × 840 mg	26	26 × 840 mg
nab-paclitaxel	100 mg/m² = 176 mg		2 × 100 mg	39	78 × 100 mg
Appropriate comparator therapy: a therapy containing anthracycline and/or taxane					
Docetaxel					
Docetaxel	100 mg/m² = 176 mg	176 mg	1 × 160 mg + 1 × 20 mg	17.4	17.4 × 160 mg + 17.4 × 20 mg
Docetaxel + capecitabine					
Docetaxel	75 mg/m² = 132 mg	132 mg	1 × 140 mg +	17.4	17.4 × 140 mg +
Capecitabine	1,250 mg/m² = 2200 mg	2500 mg/m² = 4400 mg	8 × 500 mg + 2 × 300 mg	243.6	1948.8 × 500 mg + 487.2 × 300 mg
Doxorubicin					
Doxorubicin	80 mg/m² = 140.8 mg –	140.8 mg	1 × 150 mg –	5 –	5 × 150 mg –

Designation of the therapy	Dosage/ use	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	50 mg/m² = 88 mg	88 mg	1 × 100 mg	11	11 × 100 mg
Doxorubicin + docetaxel					
Doxorubicin	50 mg/m² = 88 mg –	88 mg–	1 × 100 mg	9 – 11	9 × 100 mg – 11 × 100 mg
Docetaxel	75 mg/m² = 132 mg	132 mg	1 × 140 mg	17.4	17.4 × 140 mg
Doxorubicin + cyclophosphamide					
Doxorubicin	60 mg/m² = 105.6 mg –	88 mg–	1 × 100 mg + 1 × 10 mg	7 – 9	7 × 100 mg + 7 × 10 mg – 9 × 100 mg + 9 × 10 mg
Cyclophosphamide	600 mg/m² = 1056 mg	1056 mg	1 × 1,000 mg + 1 × 200 mg	17.4	17.4 × 1,000 mg + 17.4 × 200 mg
Doxorubicin + paclitaxel					

Designation of the therapy	Dosage/ use	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Doxorubicin	50 mg/m² = 88 mg –	88 mg–	1 × 100 mg	9 –	9 × 100 mg –
				11	11 × 100 mg
Paclitaxel	220 mg/m² = 387.2 mg	387.2 mg	1 × 300 mg +	17.4	17.4 × 300 mg +
			1 × 100 mg		17.4 × 100 mg
Doxorubicin (pegylated, liposomal)					
Doxorubicin (pegylated, liposomal)	50 mg/m² = 88 mg	88 mg	2 × 20 mg +	13	26 × 20 mg +
			1 × 50 mg		13 × 50 mg
Liposomal doxorubicin + cyclophosphamide					
Liposomal doxorubicin	60 mg/m² = 105.6 mg –	105.6 mg –	3 × 50 mg	17.4	52.2 × 50 mg
	75 mg/m² = 132 mg	132 mg			
Cyclophosphamide	600 mg/m² = 1056 mg	1056 mg	1 × 1,000 mg +	17.4	17.4 × 1,000 mg +

Designation of the therapy	Dosage/ use	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
			1 × 200 mg		17.4 × 200 mg
Epirubicin					
Epirubicin	90 mg/m² = 158.4 mg –	158.4 mg	1 × 150 mg +	10 –	10 × 150 mg +
			1 × 10 mg –		10 × 10 mg –
	60 mg/m² = 105.6 mg	105.6 mg	1 × 100 mg +	16	16 × 100 mg +
			1 × 10 mg		16 × 10 mg
Epirubicin + cyclophosphamide					
Epirubicin hydrochloride	75 mg/m² = 132 mg	132 mg	1 × 150 mg –	13 –	13 × 150 mg –
	60 mg/m² = 105.6 mg –	105.6 mg	1 × 100 mg +	15	15 × 100 mg +
			1 × 10 mg		15 × 10 mg
Cyclophosphamide	600 mg/m² = 1056 mg	1056 mg	1 × 1,000 mg +	17.4	17.4 × 1,000 mg +
			1 × 200 mg		17.4 × 200 mg

Designation of the therapy	Dosage/ use	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Epirubicin + docetaxel					
Epirubicin	75 mg/m² = 132 mg	132 mg	1 × 150 mg	12 – 13	12 × 150 mg – 13 × 150 mg
Docetaxel	75 mg/m² = 132 mg	132 mg	1 × 140 mg +	17.4	17.4 × 140 mg +
Epirubicin + paclitaxel					
Epirubicin	60 mg/m² = 105.6 mg –	105.6 mg	1 × 100 mg + 1 × 10 mg	15–16	15 - 16 × 100 mg + 15–16 × 10 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 × 300 mg + 1 × 30 mg	17.4	17.4 × 300 mg + 17.4 × 30 mg
Paclitaxel					
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 × 300 mg + 1 × 30 mg	17.4	17.4 × 300 mg + 17.4 × 30 mg

Designation of the therapy	Dosage/ use	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Gemcitabine + paclitaxel					
Gemcitabine	1,250 mg/m² = 2200 mg	2200 mg	1 × 2200 mg	34.8	34.8 × 2200 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 × 300 mg + 1 × 30 mg	17.4	17.4 × 300 mg + 17.4 × 30 mg

Costs:

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 840 mg	1 CIS	€ 3,301.64	€ 1.77	€ 185.28	€ 3,114.59
nab-paclitaxel 100 mg	1 PIS	€ 429.09	€ 1.77	€ 52.91	€ 374.41
Appropriate comparator therapy					
Capecitabine 300 mg[6]	120 FCT	€ 95.91	€ 1.77	€ 6.72	€ 87.42
Capecitabine 500 mg[6]	120 FCT	€ 151.57	€ 1.77	€ 11.12	€ 138.69
Cyclophosphamide 1,000 mg	6 PIJ	€ 123.70	€ 1.77	€ 6.24	€ 115.69
Cyclophosphamide 200 mg	10 PIJ	€ 60.98	€ 1.77	€ 2.77	€ 56.44
Docetaxel 140 mg	1 CIS	€ 1,145.74	€ 1.77	€ 53.85	€ 1,090.12
Docetaxel 160 mg	1 CIS	€ 1,397.36	€ 1.77	€ 175.44	€ 1,220.15

[6] Fixed reimbursement rate

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
Docetaxel 20 mg	1 CIS	€ 172.41	€ 1.77	€ 7.66	€ 162.98
Doxorubicin 10 mg[6]	1 CIS	€ 40.04	€ 1.77	€ 2.29	€ 35.98
Doxorubicin 100 mg[6]	1 CIS	€ 285.52	€ 1.77	€ 0.00	283.75
Doxorubicin 150 mg[6]	1 SFI	€ 418.08	€ 1.77	€ 0.00	416.31
Liposomal doxorubicin	1 DSS	€ 1,250.95	€ 1.77	€ 167.12	€ 1,082.06
Doxorubicin (pegylated, liposomal) 20 mg	1 CIS	€ 762.06	€ 1.77	€ 41.58	€ 718.71
Doxorubicin (pegylated, liposomal) 50 mg	1 CIS	€ 1,877.65	€ 1.77	€ 103.96	€ 1,771.92
Epirubicin 10 mg	1 SFI	€ 39.23	€ 1.77	€ 1.34	€ 36.12
Epirubicin 10 mg	1 SFI	€ 39.17	€ 1.77	€ 1.34	€ 36.06
Epirubicin 100 mg	1 SFI	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Epirubicin 150 mg	1 SFI	€ 445.12	€ 1.77	€ 20.60	€ 422.75
Gemcitabine 2,200 mg	1 IS	€ 495.56	€ 1.77	€ 22.99	€ 470.80
Paclitaxel 100 mg	1 CIS	€ 361.26	€ 1.77	€ 16.62	€ 342.87
Paclitaxel 30 mg	1 CIS	€ 115.51	€ 1.77	€ 4.96	€ 108.78
Paclitaxel 300 mg	1 CIS	€ 1,045.32	€ 1.77	€ 49.08	€ 994.47
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; IS = infusion solution; PIS = powder for the preparation of an infusion solution; PIJ = powder for the preparation of an infusion solution; DSS = dry substance with solvent					

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.

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							
Paclitaxel							
Dexamethasone 20 mg[7]	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
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; TAB = tablets							

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.

[7] Fixed reimbursement rate

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 22 March 2016.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 31 July 2019.

On 19 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 2, sentence 2 VerfO.

By letter dated 20 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 27 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.

By letter dated 10 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 12 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	22 March 2016	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, Commissioning of the IQWiG with the supplementary assessment of documents

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