Justification

Gemeinsamer Bundesausschuss

of 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: hepatocellular carcinoma, combination with bevacizumab)

of 20 May 2021

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 studies 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:

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

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

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

2. Key points of the resolution

The active ingredient Atezolizumab (tecentriq) was listed for the first time on 1 October 2017 in the “LAUER-TAXE®”, the extensive German registry of available medicinal products and their prices.

On 27 October 2020, Atezolizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2a letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of amendments 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 23 November 2020, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company on the approval of a new area of application, the pharmaceutical company has 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

“Atezolizomab in combination with bevacizumab in adult patients for the treatment of advanced or unresectable hepatocellular carcinoma who have not received prior systemic treatment.”

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 March 2021 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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

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

2.1.1 Approved therapeutic indication of Atezolizumab (tecentriq) in accordance with the product information

Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

Therapeutic indication of the resolution (resolution of 20/05/2021):

see approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with advanced HCC with Child-Pugh A or no cirrhosis without prior systemic therapy

Appropriate comparator therapy for Atezolizumab in combination with bevacizumab:

- Sorafenib or lenvatinib

b) Adult patients with advanced HCC with Child-Pugh B without previous systemic therapy

Appropriate comparator therapy for Atezolizumab in combination with bevacizumab:

- Best supportive care

[1] General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the 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 approval status, the active agents sorafenib, mitomycin and lenvatinib are available for the first-line therapy of hepatocellular carcinoma.

on 2. A non-medicinal therapy cannot be considered as an appropriate comparator therapy in this therapeutic indication.

For the present field of application, it is assumed that both curative treatment (corresponding to BCLC stages 0 and A) and locoregional therapy in BCLC stage B, in particular transarterial (chemo)-embolisation (TACE or TAE), are not (no longer) considerable.

on 3. For the present indication of Atezolizumab in combination with bevacizumab, the following decision of the G-BA for drug applications is available:

- Lenvatinib – Resolution of 22 March 2019

on 4. The generally accepted state of medical knowledge on which the GB-A findings are based was represented in the present therapeutic indication by means of a systematic search for guidelines and reviews of clinical studies.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V.

According to the available evidence, the stage of the disease and the functional capacity of the liver mainly determine the treatment decision for first-line treatment of hepatocellular carcinoma.

For the present therapeutic indication, it is assumed that both curative treatment (corresponding to BCLC stages 0 and A) and locoregional therapy in BCLC stage B, in particular transarterial (chemo)-embolisation (TACE or TAE), are not (no longer) considerable. It is also anticipated that patients with BCLC stage D will not be eligible for therapy with Atezolizumab in combination with bevacizumab.

Patient group a)

According to current guidelines, systemic therapy may be considered for patients with stage B or C hepatocellular carcinoma and preserved liver function (Child-Pugh stage A). According to the available evidence for first-line therapy in this indication, both sorafenib and lenvatinib can be considered as a standard therapy. Sorafenib showed a survival benefit over placebo and was approved in 2007. For lenvatinib, which is still relatively new, the G-BA did not identify any additional benefit over sorafenib in the benefit assessment for patients with Child-Pugh A or no liver cirrhosis without prior systemic therapy. Guidelines recommend lenvatinib for first-line treatment of hepatocellular carcinoma according to its marketing authorisation. In addition, according to medical experts, sorafenib has a specific, therapy-limiting side effect profile, from which the specific side effect profile of lenvatinib differs qualitatively, which justifies the place of lenvatinib in the present field of application in the care. Lenvatinib is therefore considered to be another equally suitable appropriate comparator therapy alongside sorafenib, although no additional benefit was identified for lenvatinib in the benefit assessment.

Patient group b

Based on the available evidence and the comments in current guidelines, systemic therapy cannot be recommended for patients with impaired liver function (Child-Pugh stage B cirrhosis). Therefore, only best supportive care for patients with Child-Pugh stage B is considered an appropriate comparator therapy.

Best Supportive Care is the therapy that provides the best possible supportive treatment, optimised for each individual patient, to alleviate symptoms and improve quality of life.

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

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 advanced HCC with Child-Pugh A or no cirrhosis without prior systemic therapy

Indication of a considerable additional benefit

b) Adult patients with advanced HCC with Child-Pugh B without previous systemic therapy

An additional benefit is not proven.

Justification:

Description of the study IMbrave150

For the proof of additional benefit of Atezolizumab in combination with bevacizumab compared to sorafenib, the pharmaceutical company has presented results from the open-label, randomised controlled phase III study IMbrave150.

The study included adult patients with locally advanced or metastatic and/or unresectable HCC who had not previously received systemic therapy. Further requirements for study inclusion were a Child-Pugh stage A classification and a general condition according to ECOG-PS of 0 or 1.

In the global cohort, 501 patients were randomly assigned to treatment with atezolizumab + bevacizumab (N = 336) or with sorafenib (N = 165) in a 2:1 ratio. Stratification was performed by region (Asia excluding Japan/rest of the world), macrovascular invasion and/or extrahepatic spread (present/absent), alpha-fetoprotein (AFP; < 400 ng/ml/≥ 400 ng/ml), ECOG-PS (0/1). In addition to this global cohort, there was a Chinese cohort ("China extension cohort") with an identical study protocol. The Chinese cohort (N = 194) has a very large overlap of n = 137 with the global cohort. Only 57 patients were evaluated in the Chinese cohort only. Data from the Chinese cohort were analysed in a separate study report. The pharmaceutical company uses only the results of the global cohort to derive the added benefit on the grounds that the additional 57 patients of the "China expansion cohort" were not part of the data for the EMA approval. IQWiG's benefit assessment considers the patients in the Chinese cohort who are not part of the global cohort (n = 57) as a relevant subpopulation of the IMbrave150 study. In the dossier, the pharmaceutical company presented corresponding summary analyses based on individual patient data, which include all patients included in the IMbrave150 study (total population: 501 patients in the global cohort + 57 patients in the Chinese cohort who are not concurrent patients in the global cohort). These analyses were included in the benefit assessment.

Treatment was given until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, or death.

Co-primary endpoints in the study were Overall survival and Progression-free survival. Patient-relevant secondary endpoints were Overall survival, Morbidity, Health-related quality of life, and Adverse events.

In the global cohort, analyses are available for the following data cut-offs:

- 1. Data cut-off as of 29/8/2019: primary analysis of PFS and final analysis of overall survival
- FDA 3-month safety update as of 29/11/2019; evaluations for AEs only
- 2. Data slice as of 31/08/2020: Analysis of, among other things, Overall survival and PFS as part of the approval process at the request of the EMA

In the Chinese cohort, analyses are available for the following data cut-offs:

- 1. Data slice as of 29/08/2019: Analysis of PFS (planned at the time of the primary analysis of PFS in the global cohort)

The pharmaceutical company submitted data on overall survival for the total population (501 patients from the global cohort + 57 patients from the Chinese cohort who are not also patients in the global cohort) of the IMbrave150 study at the data cut-off date of 31 August 2020. Therefore, the benefit assessment is basically based on the combined analysis of both cohorts (total population: 501 patients in the global cohort + 57 patients in the Chinese cohort who are not concurrent patients in the global cohort) of the IMbrave150 study.

On PD-L1 expression status

For the benefit assessment, no evaluations with regard to PD-L1 expression were submitted by the pharmaceutical company. Exploratory PD-L1 expression analysis of 40% of patients from the IMbrave150 study suggests that patients with higher PD-L1 expression (≥ 1%) benefit more in terms of efficacy than patients with negative PD-L1 expression status (< 1%). In this

regard, the EMA points out in the EPAR[2] that no reliable conclusions can be drawn from this exploratory analysis because appropriate biopsies are only available from 40% of patients and therefore calls for further evaluation of efficacy data according to PD-L1 expression status of Atezolizumab + bevacizumab compared to sorafenib.

Given the known predictive value of PD-L1 expression for treatment with Atezolizumab in other indications, data in relation to this would have been desirable.

Extent and probability of the additional benefit

a) Adult patients with advanced HCC with Child-Pugh A or no cirrhosis without prior systemic therapy

Mortality

Overall survival was one of the co-primary efficacy endpoints in the IMbrave150 study and was defined as the time between randomisation and death from any cause.

Overall survival in the total population at the 31/8/2020 data cut-off was statistically significantly prolonged in the Atezolizumab + bevacizumab treatment group compared with the control group.

Thereby, an effect modification is shown in the subgroup analyses for the characteristic aetiology of HCC. For patients with viral aetiology of HCC, overall survival showed a statistically significant difference to the benefit of Atezolizumab + bevacizumab compared to sorafenib. In contrast, there was no statistically significant difference for the subgroup of patients with non-viral aetiology.

In view of the fact that overall meaningful data on overall survival are available in the IMbrave150 study, the additional benefit is derived on the basis of the results at the data cut-off of 31/08/2020 for the patients in the overall study population.

Treatment with Atezolizumab + bevacizumab shows a prolongation of survival compared to treatment with sorafenib, which is assessed as a significant improvement.

Subgroup analysis for the HCC aetiology characteristic was prespecified in the IMbrave150 study; the HCC aetiology characteristic was not used as a stratification factor for randomisation.

The effect modification by the characteristic aetiology of HCC was observed in the subgroup analysis in the endpoint overall survival and was not evident in any other endpoint beyond that.

Taking into account the comments of the medical experts on the subgroup results for patients with viral aetiology and non-viral aetiology of HCC, these are not considered to be sufficiently robust to make a correspondingly separate assessment of additional benefit in the overall assessment. These subgroup results are nevertheless considered a relevant outcome of the benefit assessment.

Morbidity

Progression-free survival

[2] European Medicines Agency. CHMP extension of indication variation assessment report: Tecentriq. 17 September 2020, pages 122 and 123

Progression-free survival (PFS) was one of the co-primary efficacy endpoints in the study. It was defined as the time between randomisation and the time of first disease progression or death from any cause, whichever occurred earlier. Disease progression was assessed according to the RECIST criteria v1.1.

PFS was statistically significantly prolonged in the Atezolizumab + bevacizumab treatment group compared with the control group.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component “Mortality” was collected in the IMbrave150 study via the endpoint “overall survival” as an independent endpoint. The morbidity component “Disease progression” was assessed solely by means of imaging procedures (radiologically determined disease progression according to the RECIST criteria). Thus, morbidity is not primarily assessed on the basis of disease symptoms, but solely on the basis of asymptomatic findings that are not directly relevant to the patient.

Taking into consideration the aforementioned aspects, there are different views within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology

The symptomatology of the IMbrave study patients assessed using the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires.

For the present assessment, the evaluation of the time until the first deterioration of symptoms is used (increase of the score by at least 10 points compared to the initial value).

For the symptom scales Nausea and vomiting, Dyspnoea, Loss of appetite, Constipation, Diarrhoea of the EORTC QLQ-C30, the symptom scales jaundice, abdominal swelling of the EORTC QLQ-HCC18, and the symptom scales Fatigue of the EORTC QLQ-C30 as well as EORTC QLQ-HCC18, there is a statistically significant difference for the benefit of Atezolizumab + bevacizumab compared to sorafenib.

The symptom scale Pain is assessed by both the EORTC QLQ-C30 and the -HCC18 questionnaire. For both symptom scales, there was a statistically significant difference in the benefit of Atezolizumab + bevacizumab over sorafenib.

For the symptom scales Insomnia of the EORTC QLQ-C30 as well as the symptom scale Fever of the EORTC QLQ-HCC18 there was no statistically significant difference between the treatment groups.

The overall results show a relevant improvement in symptoms through positive effects on many endpoints under treatment with Atezolizumab + bevacizumab compared to treatment with sorafenib.

Health status (EQ-5D VAS)

In the IMbrave150 study, health status was assessed using the EQ-5D VAS questionnaire.

In the dossier, the pharmaceutical company presented responder analyses operationalised as time to first worsening, defined as a decrease in score by ≥ 10 points compared with baseline. These responder analyses are used for the benefit assessment.

In the responder analysis, a statistically significant difference in favour of Atezolizumab + bevacizumab compared to sorafenib was shown for the endpoint Health status at a MID of 10 points.

With its statement, the pharmaceutical company submitted responder analyses for the period up to the first deterioration by 15 points. These responder analyses are also used for the benefit assessment. With regard to this response criterion for the endpoint health status, there is a clear statistically significant advantage of Atezolizumab + bevacizumab compared to sorafenib.

There is therefore a significant advantage in terms of health status.

Quality of life

Health-related quality of life was assessed in the IMbrave150 study using the global health status and function scales of the EORTC QLQ-C30 and the function scales of the EORTC QLQ-HCC18 questionnaire.

The pharmaceutical company submits responder analyses for the EORTC QLQ-C30 and -HCC18 for the time to deterioration by 10 points. This evaluation is used for the benefit assessment.

For global health status and the function scales Physical function, Role function, Emotional function, Cognitive function and Social function of the EORTC QLQ-C30, as well as the function scales Body image and Nutrition of the EORTC QLQ-HCC18, there is a statistically significant difference for the benefit of Atezolizumab + bevacizumab over sorafenib in each case.

However, there were no statistically significant differences between the treatment groups for either endpoint.

Overall, a significant advantage can be derived for Atezolizumab + bevacizumab compared to sorafenib in the endpoint category Quality of life.

Side effects

Adverse event endpoints were collected for the period of treatment with the study medication plus 90 days for serious adverse events (SAEs) or plus 30 days for additional SAEs.

Adverse events (AE) in total

In the IMbrave150 study, 98.1% of patients experienced an adverse event in the intervention arm. In the comparator arm, this was 98.3% of patients.

Serious adverse events (SUE), serious AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the endpoint immune-mediated severe AEs (discontinuation AE).

Specific AE

Immune-mediated AEs and bleeding

For immune-mediated AEs, no summary analysis of events is available, but only results for individual immune-mediated AEs for Atezolizumab, which are not usable for the benefit assessment. Therefore, a conclusive assessment of immune-mediated AEs is not possible.

For the endpoints on bleeding (AEs, SAEs, severe AEs) there was no statistically significant difference between the treatment groups.

Hand Foot Syndrome

For the endpoint Hand-foot syndrome (severe AEs), there is a statistically significant difference in the benefit of Atezolizumab + bevacizumab compared to sorafenib.

Other specific AEs

For the endpoints Alopecia, Diarrhoea and increased Blood bilirubin and for the endpoints General disorders and administration site conditions, metabolism and nutrition disorders as well as diseases of the respiratory tract, thoracic and mediastinal disorders, a statistically significant difference to the advantage of Atezolizumab + bevacizumab compared to sorafenib was shown in each case.
For the endpoint Infections and infestations, there is a statistically significant difference to the disadvantage of Atezolizumab + bevacizumab compared to sorafenib.

Overall, there was no statistically significant difference in adverse events between the study arms with respect to the endpoints Serious AEs, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to AEs. In detail, specific AEs show both positive and negative effects of Atezolizumab + bevacizumab compared to sorafenib. For a complete assessment of side effects, a summary analysis of immune-mediated side effects suitable for the benefit assessment would be required.

<u>Overall assessment/conclusion</u>

For the evaluation of the additional benefit of Atezolizumab + bevacizumab versus sorafenib in the population of patients with advanced HCC with Child-Pugh A or no liver cirrhosis, results on mortality (overall survival), morbidity (symptoms and health status), health-related quality of life and side effects are available from the open-label, randomised, controlled study IMbrave150.

In the endpoint category Mortality, the present results for the endpoint Overall survival show a statistically significant prolongation of survival compared to treatment with sorafenib, which is assessed as a significant improvement.

In addition, a subgroup analysis for the characteristic aetiology of HCC shows an effect modification. For patients with viral aetiology of HCC, overall survival showed a statistically significant difference in favour of Atezolizumab + bevacizumab compared to sorafenib. In contrast, there was no statistically significant difference for the subgroup of patients with non-viral aetiology.

The available subgroup results on the aetiology of HCC are currently not considered sufficiently robust to allow a corresponding separate assessment of additional benefit.

In the Morbidity category, there were relevant improvements in symptomatology (assessed by EORTC QLQ-C30 and EORTC QLQ-HCC18) due to positive effects on many endpoints and in health status (assessed by EQ 5D-VAS) under Atezolizumab + bevacizumab compared to sorafenib.

For health-related quality of life, positive effects of treatment with Atezolizumab + bevacizumab versus sorafenib were also seen for the patient-reported endpoints of Global health status, Physical function, Role function, Emotional function, Cognitive function and Social function, Body image, and Nutrition. In the category of Health-related quality of life, there is a significant advantage of Atezolizumab + bevacizumab compared to sorafenib.

There were no statistically significant differences in adverse events between the study arms with regard to the endpoints Serious AEs, Serious adverse events (CTCAE grade ≥ 3) and

Discontinuation due to AEs. In detail, specific AEs show both positive and negative effects of Atezolizumab + bevacizumab compared to sorafenib. With regard to the endpoint category Adverse events, overall there are neither advantages nor disadvantages for Atezolizumab + bevacizumab compared to sorafenib.

In the overall assessment of the available results, the G-BA found a considerable additional benefit for Atezolizumab + bevacizumab compared to sorafenib.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open, randomised phase III IMbrave-150 study.

Since the benefit assessment is based on the results of only one study, only indications of an additional benefit can be derived with regard to the reliability of the results.

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

For the endpoint Overall survival, uncertainties exist regarding the effect of Atezolizumab in combination with bevacizumab due to effect modification by the characteristic “aetiology of HCC”.

The results for the endpoint categories Morbidity and Health-related quality of life are highly reliable due to the large extent of positive effects shown in many individual items of the EORTC questionnaires.

In the endpoint category Adverse events, the open study design contributes to a high risk of bias, especially in the case of discontinuation due to AEs. In addition, there is a lack of suitable evaluations of immune-mediated side effects for a comparative benefit assessment, which reduces the reliability of information on the evaluation of side effects.

In the overall assessment, despite the uncertainties mentioned, the reliability of the additional benefit identified is classified as indicative.

b) Adult patients with advanced HCC with Child-Pugh B without previous systemic therapy

No data are available to assess the added benefit of Atezolizumab + bevacizumab versus the appropriate comparator therapy in adult patients with advanced HCC with Child-Pugh B without previous systemic therapy.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient Atezolizumab. The therapeutic indication assessed here is as follows:

“Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.”

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

a) Adult patients with advanced HCC with Child-Pugh A or no cirrhosis without prior systemic therapy

b) Adult patients with advanced HCC with Child-Pugh B without previous systemic therapy

Patient population a)

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

- Sorafenib or lenvatinib

For this patient group, the pharmaceutical company presents the RCT IMbrave150, in which Atezolizumab in combination with bevacizumab was compared to sorafenib.

In the endpoint category Mortality, the present results for the endpoint Overall survival show a statistically significant prolongation of survival compared to treatment with sorafenib, which is assessed as a significant improvement.

In addition, a subgroup analysis for the characteristic aetiology of HCC shows an effect modification. For patients with viral aetiology of HCC, overall survival showed a statistically significant difference in favour of atezolizumab + bevacizumab compared to sorafenib. In contrast, there was no statistically significant difference for the subgroup of patients with non-viral aetiology.

The available subgroup results on the aetiology of HCC are currently not considered sufficiently robust to allow a corresponding separate assessment of additional benefit.

In the Morbidity category, there were relevant improvements in symptomatology due to positive effects on many endpoints and in health status under Atezolizumab + bevacizumab compared to sorafenib.

In the category of Health-related quality of life, there is a significant advantage of Atezolizumab + bevacizumab compared to sorafenib.

With regard to the endpoint category Adverse events, overall there are neither advantages nor disadvantages for Atezolizumab + bevacizumab compared to sorafenib.

In the overall assessment of the available results, the G-BA found a considerable additional benefit for atezolizumab + bevacizumab compared to sorafenib.

Despite uncertainties, an indication can be derived with regard to the reliability of the statements.

Overall, therefore, an indication of a considerable additional benefit is identified for Atezolizumab in combination with bevacizumab.

Patient population b

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

- Best supportive care

No data are available from the IMbrave150 study on which to base an assessment of the patient population.

Thus, an additional benefit for Atezolizumab in combination with bevacizumab is not proven.

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 decision is based on the data from IQWiG's dossier assessment and data submitted by the pharmaceutical company in the written statement procedure.

The range of patient numbers in the SHI target population reported in the dossier assessment (1,712 to 4,390 patients) is slightly lower than that reported in the previous 2018 study of lenvatinib in the same therapeutic area (2,438 to 4,785 patients). This is mainly due to the lower proportion of patients with HCC in those with liver cancer and the significantly lower range for the proportion of patients with BCLC stage C. In addition, although the lenvatinib study did not take into account newly diagnosed patients from previous years, the upper limit was calculated based on the sum of incidence and 1 year prevalence for the year under review.

The lower limit in the assessment on lenvatinib was judged to be underestimated due to methodological shortcomings. In the present study of Atezolizumab, these shortcomings are remedied by taking into account the progressive patient group from previous years. In addition, the pharmaceutical company uses more recent data for the proportion of patients with HCC.

The information on patient numbers submitted by the pharmaceutical company in the comments procedure takes into account a broader range for the proportion of patients with BCLC stage C (24.3% to 46.0%). This takes account of uncertainty to a greater extent. This results in a higher upper limit (4,961 patients) and an overall wider range for the number of patients in the SHI target population.

In summary, the lower limit of patients identified is a more plausible estimate than in the lenvatinib study. Using the wider range for the proportion of patients with BCLC stage C results in a higher upper limit, which is of the same order of magnitude as the upper limit reported in the dossier for lenvatinib.

Overall, the lower and upper limits are within a plausible range.

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: 27 January 2021):

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

Treatment with Atezolizumab should only be initiated and monitored by specialists in gastroenterology and others participating in the Oncology Agreement who are experienced in the treatment of patients with hepatocellular carcinoma.

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 and the patient passport contain, in particular, instructions on the management of immune-mediated side effects potentially occurring with Atezolizumab as well as on infusion-related reactions.

Patients treated with bevacizumab have an increased risk of bleeding. Patients with HCC should be screened for oesophageal varices prior to initiation of treatment with Atezolizumab in combination with bevacizumab and their subsequent treatment according to clinical practice.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2021).

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”, time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied (average body weight: 77.0 kg).[3]

The annual treatment costs shown refer to the first year of treatment.

Treatment duration:

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ year
Medicinal product to be assessed				
Patient population a)				
Atezolizumab	once per 21 day cycle	17.4	1	17.4
Bevacizumab	once per 21 day cycle	17.4	1	17.4
Patient population b)				
Atezolizumab	once per 21 day cycle	17.4	1	17.4
Bevacizumab	once per 21 day cycle	17.4	1	17.4
Best supportive care	varies from patient to patient			
Appropriate comparator therapy				
Patient population a)				

[3] Statistisches Bundesamt (Federal Statistic Office), Wiesbaden 2018: http://www.gbe-bund.de/

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ year
Lenvatinib	continuously, once daily	365	1	365
Sorafenib	continuously, twice daily	365	1	365
Patient population b)				
Best supportive care	varies from patient to patient			

Consumption:

Name of therapy	Dosage/ application	Dosage/ patient/days of treatment	Usage by strength/day of treatment	Days of treatment/ patient/ year	Average annual consumption by strength
Medicinal product to be assessed					
Patient population a)					
Atezolizumab	1,200 mg	1,200 mg	once 1,200 mg	17.4	17.4 x 1,200 mg
Bevacizumab	15 mg/kg = 1,155 mg	1,155 mg	3 x 400 mg	17.4	52.2 x 400 mg
Patient population b)					
Atezolizumab	1,200 mg	1,200 mg	once 1,200 mg	17.4	17.4 x 1,200 mg
Bevacizumab	15 mg/kg = 1,155 mg	1,155 mg	3 x 400 mg	17.4	52.2 x 400 mg
Best supportive care	varies from patient to patient				
Appropriate comparator therapy					
Patient population a)					
Lenvatinib	12 mg	12 mg	3 x 4 mg	365	1,095 x 4 mg
Sorafenib	400 mg	800 mg	4 x 200 mg	365	1,460 x 200 mg
Patient population b)					

Name of therapy	Dosage/ application	Dosage/ patient/days of treatment	Usage by strength/day of treatment	Days of treatment/ patient/ year	Average annual consumption by strength
Best supportive care	varies from patient to patient				

Costs:

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

Costs of the medicinal product:

Name of therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Atezolizumab 1,200 mg	1 IFC	€ 4,128.95	€ 1.77	€ 232.53	€ 3,894.65
Bevacizumab 400 mg	1 IFC	€ 1,553.06	€ 1.77	€ 85.42	€ 1,465.87
Best supportive care	varies from patient to patient				
Appropriate comparator therapy					
Lenvatinib 4 mg	30 HKP	€ 1,626.28	€ 1.77	€ 89.60	€ 1,534.91
Sorafenib 200 mg	112 FCT	€ 4,874.38	€ 1.77	€ 275.10	€ 4,597.51
Best supportive care	varies from patient to patient				
Abbreviations: FTA = film-coated tablets; HKP = hard capsules; IFK = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 May 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator

therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

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

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe)(Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), all surcharges for the production of parenteral preparations containing cytostatic drugs a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating in the special agreement on contractual unit costs of retail pharmacist services (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 sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs retail pharmacist services (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 08 September 2020.

On 23 November 2020, 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 24 November 2020 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 25 February 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2021. The deadline for submitting written statement procedures was 22 March 2021.

The oral hearing was held on 6 April 2021.

By letter of 07 April 2021, 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 29 April 2021.

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 11 May 2021, and the draft resolution was approved.

At its session on 20 May 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	08 September 2020	Determination of the appropriate comparator therapy
Working group Section 35a	30 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	06 April 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 April 2021 20 April 2021 4 May 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	11 May 2021	Concluding consultation of the draft resolution
Plenum	20 May 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 May 2021

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

Prof. Hecken