Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Tremelimumab (hepatocellular carcinoma, first-line, combination with durvalumab)

of 5 October 2023

Contents

1. Legal basis 2

2. Key points of the resolution 2

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy 3

2.1.1 Approved therapeutic indication of Tremelimumab (Imjudo) in accordance with the product information 3

2.1.2 Appropriate comparator therapy 3

2.1.3 Extent and probability of the additional benefit 6

2.1.4 Summary of the assessment 11

2.2 Number of patients or demarcation of patient groups eligible for treatment 12

2.3 Requirements for a quality-assured application 12

2.4 Treatment costs 13

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product 17

3. Bureaucratic costs calculation 21

4. Process sequence 22

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 the statutory health insurance funds,
6. requirements for a quality-assured application.

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

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

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient tremelimumab on 1 April 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 30 March 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on the G-BA website (www.g-ba.de) on 3 July 2023, 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 tremelimumab 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 tremelimumab.

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 Tremelimumab (Imjudo) in accordance with the product information

IMJUDO in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

Therapeutic indication of the resolution (resolution of 5 October 2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

Appropriate comparator therapy for tremelimumab in combination with durvalumab:

− Atezolizumab in combination with bevacizumab

b) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

Appropriate comparator therapy for tremelimumab in combination with durvalumab:

− Best supportive care

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

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

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

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

on 1. In addition to tremelimumab, medicinal products with the following active ingredients are approved in the therapeutic indication: sorafenib, mitomycin, lenvatinib, atezolizumab and durvalumab.

on 2. A non-medicinal therapy cannot be considered as an appropriate comparator therapy. 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) considered.

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

- Lenvatinib: Resolution of 22 March 2019
- Cabozantinib: Resolution of 6 June 2019
- Ramucirumab: Resolution of 20 February 2020
- Atezolizumab: Resolution of 20 May 2021

Annex VI to Section K of the Pharmaceuticals Directive – Active ingredients that cannot be prescribed for off-label use:

- octreotide in hepatocellular carcinoma

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

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

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

For use as first-line therapy, 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) considered.

It is also assumed that patients with BCLC stage D are not eligible for therapy with tremelimumab in combination with durvalumab.

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. Against this background, it is considered appropriate to differentiate the determination of the appropriate comparator therapy according to the following patient groups:

a) <u>Adults with unresectable hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis, first-line therapy</u>

According to the generally accepted state of medical knowledge, patients with hepatocellular carcinoma in stage BCLC B or C and with preserved liver function (Child-Pugh score A) are eligible for systemic therapy. Furthermore, according to the available evidence, a change has taken place in the mentioned patient group or treatment setting with regard to the therapy standard.

On 27 October 2020, atezolizumab in combination with bevacizumab was approved for the treatment of advanced or unresectable hepatocellular carcinoma in adult patients who have not received prior systemic treatment. By resolution of 20 May

2021, based on the data from the IMbrave150 study, the G-BA identified an indication of a considerable additional benefit over sorafenib in the benefit assessment of atezolizumab in combination with bevacizumab in patients with Child-Pugh A or no liver cirrhosis who have not received prior systemic treatment.

According to current guidelines, the relevant patients should be offered first-line therapy with atezolizumab in combination with bevacizumab. According to the statements by the scientific-medical societies, systemic therapy with atezolizumab in combination with bevacizumab is also to be considered the current standard for this patient group.

Thus, according to the generally accepted state of medical knowledge, a first-line therapy with atezolizumab in combination with bevacizumab represents the new therapy standard compared to the two previously established therapy options sorafenib and lenvatinib. Sorafenib had already been approved in 2007 and had shown a survival advantage over placebo; by resolution of 22 March 2019, the G-BA had not identified any additional benefit of lenvatinib over sorafenib in the benefit assessment for patients with Child-Pugh A or no liver cirrhosis without prior systemic therapy.

According to the guidelines and the statements by the scientific-medical societies, lenvatinib or sorafenib only assume significance as alternatives to first-line therapy in patients with a contraindication to atezolizumab in combination with bevacizumab.

b) Adults with unresectable hepatocellular carcinoma (HCC) with Child-Pugh B, first-line therapy

According to the generally accepted state of medical knowledge, antineoplastic systemic therapy is generally only recommended for patients in Child-Pugh score A. Furthermore, it is recommended offering systemic therapy with sorafenib also in Child-Pugh score B (up to 8 points) only in individual cases. This recommendation is only an open recommendation (recommendation grade 0) for sorafenib. Sorafenib is therefore not considered as an appropriate comparator therapy.

Only best supportive care for patients with Child-Pugh score B is determined as the appropriate comparator therapy. Best supportive care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment 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 mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

a) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

An additional benefit is not proven.

Justification:

In the absence of direct comparator studies of tremelimumab in combination with durvalumab versus the appropriate comparator therapy, the pharmaceutical company uses an adjusted indirect comparison according to the procedure of Bucher et al. for the proof of an additional benefit. For the adjusted indirect comparison via the bridge comparator of sorafenib, the pharmaceutical company includes the HIMALAYA study on the side of tremelimumab in combination with durvalumab and the IMbrave150 study on the side of atezolizumab + bevacizumab.

Description of the HIMALAYA study

The HIMALAYA study is an open-label randomised controlled trial comparing durvalumab in combination with tremelimumab or durvalumab as monotherapy versus sorafenib with 4 treatment arms. For the present benefit assessment, the comparison of durvalumab + tremelimumab versus sorafenib is used. The study ongoing since 2017 is being conducted in 170 study sites in North and South America, Europe and Asia.

Adults with advanced or unresectable HCC who are ineligible for locoregional therapy and had not received prior systemic therapy for HCC were enrolled in the study. Further requirements for enrolment in the study were a Barcelona Clinic Liver Cancer (BCLC) stage B or C, as well as a Child-Pugh score A and an Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) of 0 or 1.

A total of 782 patients were allocated to the study arms durvalumab + tremelimumab (393 patients) and sorafenib arm (389 patients), stratified by macrovascular invasion (yes/ no), aetiology of liver disease (hepatitis B/ hepatitis C/ other) and ECOG-PS (0/ 1). A planned extension cohort in China was not considered in the benefit assessment.

In both the relevant intervention arm and the comparator arm, the patients were treated largely according to the requirements in the product information. There were deviations with regard to the re-administration of tremelimumab (rechallenge) permitted according to the study protocol, followed by treatment with durvalumab after disease progression and possible dose reduction of sorafenib in the event of adverse drug reactions.

Treatment was given in both arms until disease progression, unacceptable toxicity or the occurrence of another discontinuation criterion. Under certain conditions, treatment beyond disease progression was possible.

The primary endpoint of the study was overall survival. Patient-relevant secondary endpoints were morbidity, health-related quality of life, and adverse events (AEs).

For the HIMALAYA study, 3 data cut-offs are available in total:

- 1st data cut-off from 02.09.2019: interim analysis for objective response rate and duration of response

- 2nd data cut-off from 22.05.2020: interim analysis for overall survival
- 3rd data cut-off from 27.08.2021: final analysis of overall survival

The 3rd data cut-off from 27.08.2021 is used for the benefit assessment.

Description of the IMbrave150 study

The IMbrave 150 study is an open-label, randomised controlled phase III study conducted in 111 study sites in Asia, Australia, Europe and North America from 2018 to 2022.

Adult patients with locally advanced or metastatic and/or unresectable HCC who have not previously received systemic therapy were enrolled in the study. Further requirement for enrolment in the study were a Child-Pugh score A classification and a general condition according to ECOG-PS of 0 or 1.

In total, 558 patients were randomised in a 2:1 ratio and allocated to treatment with atezolizumab + bevacizumab (N = 375) or sorafenib (N = 183) , stratified 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) and ECOG-PS (0/1).

Treatment was given according to the product information to a great extent until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, or death. Under certain conditions, treatment beyond disease progression was possible.

Co-primary endpoints in the study were overall survival and progression-free survival. Patient-relevant secondary endpoints were morbidity, health-related quality of life, and adverse events.

For the IMbrave150 study, 3 data cut-offs are available in total:

- 1st data cut-off from 29.08.2019: primary analysis of PFS and final analysis of overall survival
- 2nd data cut-off from 29.11.2019: 3-month safety update of the Food and Drug Administration (FDA): only evaluations of AEs
- 3rd data cut-off from 31.08.2020: analysis of overall survival and PFS, among other things, as part of the marketing authorisation at the request of the European Medicines Agency (EMA)

The pharmaceutical company submits evaluations for the endpoint of overall survival for the most recent data cut-off from 31.08.2020. For the endpoints of the category morbidity and health-related quality of life, results are available for the 1st data cut-off, which are not presented by the pharmaceutical company in the dossier. The analysis of AE endpoints is based on the most recent data cut-offs from 29.11.2019 (total population) and 29.08.2019 (Chinese cohort).

For indirect comparison

A core requirement for the consideration of studies in the adjusted indirect comparison via a bridge comparator is similarity.

In terms of study design, patient population and bridge comparator, the HIMALAYA and IMbrave150 studies are similar.

With regard to the similarity of the patient populations of the HIMALAYA and IMbrave150 studies, the demographic and clinical characteristics are sufficiently comparable. Differences are seen in the percentages of patients affected by macrovascular invasion and/or extrahepatic spread (HIMALAYA study approx. 66% vs IMbrave150 study approx. 76%). This is negligible as no relevant effect modifications are known for this characteristic. Larger differences between the two study populations are shown with regard to the aetiology of HCC, a known effect modifier, by infection with hepatitis B (IMbrave150 study approx. 50% vs HIMALAYA study approx. 31%) or non-viral aetiology (IMbrave150 study approx. 28% vs HIMALAYA study approx. 42%). These differences are also partly reflected in different percentages of the Asian region in the studies (HIMALAYA study approx. 40% vs IMbrave150 study 46%).

The planned observation of the endpoints on morbidity, health-related quality of life and severe AEs differs between the studies. In the present assessment, these differences in the planned duration of follow-up have no consequences for the morbidity endpoints, as there are no suitable data for the indirect comparison regardless of this.

There are differences between the sorafenib arms of the HIMALAYA and IMbrave150 studies (1st data cut-off), both for the median treatment duration (4.1 months vs 2.8 months) and for the median duration of observation for the endpoint of overall survival (13.3 months vs 10.4 months). No data are available for the treatment duration of patients in the IMbrave150 study at the 2nd data cut-off (31.08.2020), therefore it remains unclear whether the differences will also persist at this data cut-off. It is unclear how the observation durations for overall survival were calculated or estimated. Sufficient similarity of the observation durations is assumed as the actually observed median survival times for the endpoint of overall survival do not differ between the studies (13.8 vs 13.4 months).

In summary, there are partial differences in study and patient characteristics between the HIMALAYA and IMbrave150 studies, none of which, however, fundamentally calls into question the sufficient similarity to conduct an adjusted indirect comparison via the bridge comparator sorafenib.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, the adjusted indirect comparison does not show any statistically significant difference between tremelimumab + durvalumab and atezolizumab + bevacizumab. This does not provide any hint for an additional benefit of tremelimumab + durvalumab compared to atezolizumab + bevacizumab, an additional benefit is therefore not proven.

Morbidity and quality of life

For the endpoints of the categories of morbidity and quality of life, no suitable data are available for an indirect comparison.

There are differences in the observation durations in both HIMALAYA and IMbrave150 studies. Therefore, in the present situation, evaluations on time to first deterioration are to be used. However, such analyses are only available for the IMbrave150 study. Furthermore, there is a high risk of bias for all of the endpoints mentioned for morbidity and health-related quality of

life, at least due to the lack of blinding in the subjective endpoint collection, so that the requirement for certainty of results for the implementation of an adjusted indirect comparison would not be fulfilled.

Side effects

AEs total

AEs occurred in almost all patients in the HIMALAYA and IMbrave150 studies.

Serious adverse events (SAE)

For the endpoint of SAEs, the adjusted indirect comparison does not show any statistically significant difference between tremelimumab + durvalumab compared to atezolizumab + bevacizumab.

Severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

The endpoints on side effects are collected for the period of treatment with the study medication. Therefore, the duration of observation for the endpoints mentioned in both studies differs from patient to patient. For the results of the endpoint of discontinuation due to AEs, the open-label study design also leads to a high risk of bias.

Due to these limitations, there are uncertainties in the interpretation of the results for the endpoint of severe AEs from the indirect comparison.

For the endpoint of discontinuation due to AEs, an insufficient certainty results in the respective HIMALAYA and IMbrave150 studies. The requirements for an adjusted indirect comparison are therefore not met.

PRO-CTCAE, immune-mediated AEs and bleeding

The endpoints of PRO-CTCAE and bleeding were collected in the HIMALAYA and/or IMbrave150 studies, but no data on the endpoint were presented in the dossier.

For the endpoint of immune-mediated AEs, a review of the comparability of the operationalisations of immune-mediated AEs between the studies is lacking. In addition, no suitable data are available for the IMbrave150 study due to the lack of a summary analysis of immune-mediated AEs, among other reasons. For the endpoint of immune-mediated AEs, no indirect comparison is performed in the present assessment.

No suitable data or none at all are available for the endpoints of PRO-CTCAE, bleeding and immune-mediated AEs.

Overall, there is no hint for an advantage or disadvantage of tremelimumab + durvalumab compared to atezolizumab + bevacizumab in terms of side effects.

Overall assessment/ conclusion

For the assessment of the additional benefit of tremelimumab in combination with durvalumab versus atezolizumab in combination with bevacizumab in adults with advanced or unresectable HCC with Child-Pugh A or no liver cirrhosis, results are available from the adjusted indirect comparison of the HIMALAYA study with the IMbrave150 study via the bridge comparator sorafenib. The studies presented are sufficiently similar and overall suitable for conducting an adjusted indirect comparison.

For the endpoint of overall survival, there is no relevant difference for the assessment.

No suitable data are available for the endpoint categories of morbidity and quality of life.

For the endpoint category of side effects, there are no relevant differences for the assessment of the endpoint of SAE. There are uncertainties in the interpretation of the results for the endpoint of severe AEs. No suitable data are available for the endpoint of discontinuation due to AEs.

In the overall assessment, an additional benefit of tremelimumab in combination with durvalumab over atezolizumab in combination with bevacizumab in adults with advanced or unresectable HCC with Child-Pugh A or no liver cirrhosis is not proven.

b) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

An additional benefit is not proven.

Justification:

For adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh B in first-line therapy, the pharmaceutical company does not submit data for the assessment of additional benefit. Therefore, an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Imjudo with the active ingredient tremelimumab.

The therapeutic indication assessed here is as follows:

"Imjudo in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC)."

In the therapeutic indication under consideration, 2 patient groups were distinguished and the appropriate comparator therapy was determined as follows:

a) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

Appropriate comparator therapy for durvalumab in combination with tremelimumab:

− Atezolizumab in combination with bevacizumab

b) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

Appropriate comparator therapy for durvalumab in combination with tremelimumab:

− Best supportive care

Patient group a)

The pharmaceutical company presents an adjusted indirect comparison tremelimumab in combination durvalumab (HIMALAYA study) versus atezolizumab in combination with bevacizumab (IMbrave150 study) via the bridge comparator sorafenib for assessment. The studies presented are sufficiently similar and suitable for conducting an adjusted indirect comparison.

There is no relevant difference for the assessment of overall survival.

No suitable data are available for morbidity and quality of life.

For the side effects, there are no relevant differences for the assessment of the endpoint of SAE. There are uncertainties in the interpretation of the results for the endpoint of severe AEs. No suitable data are available for the endpoint of discontinuation due to AEs.

In the overall assessment, an additional benefit of durvalumab in combination with tremelimumab over atezolizumab in combination with bevacizumab in adults with advanced or unresectable HCC with Child-Pugh A or no liver cirrhosis is not proven.

Patient group b)

For adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh B in first-line therapy, the pharmaceutical company does not submit data for the assessment of additional benefit. Therefore, an additional benefit 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).

In the dossier submitted by the pharmaceutical company, there are overestimates of the baseline and the upper limit of the percentage in BCLC stage C as well as an uncertainty resulting from the percentage values transferred to the 5-year prevalence.

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of atezolizumab in combination with bevacizumab (resolution of 20 May 2021)[2]. A more valid estimate of the number of patients in the SHI target population is available here; this can be used despite continuing uncertainties.

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 Imjudo (active ingredient: tremelimumab) at the following publicly accessible link (last access: 27 June 2023):

2 Benefit assessment procedure D-603 atezolizumab in combination with bevacizumab; https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/613/#beschluesse

https://www.ema.europa.eu/en/documents/product-information/imjudo-epar-product-information_en.pdf

Treatment with tremelimumab in combination with durvalumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology as well as specialists in gastroenterology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with hepatocellular carcinoma.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient card).

The training material contains, in particular, information and warnings about symptoms of immune-mediated adverse reactions.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2023).

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 varies from patient to patient 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.

In combination with durvalumab, tremelimumab is used as a single dose only on the first day of the first cycle, followed by durvalumab monotherapy every 4 weeks.

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

Treatment period:

a) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tremelimumab + durvalumab				
Tremelimumab	Single dose on day 1 in cycle 1	1	1	1.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Durvalumab	1 x every 28 days	13	1	13.0
Appropriate comparator therapy				
Atezolizumab + bevacizumab				
Atezolizumab	1 x every 21 days	17.4	1	17.4
	or			
	1 x every 14 days	26.1	1	26.1
	or			
	1 x every 28 days	13	1	13.0
Bevacizumab	1 x every 21 days	17.4	1	17.4

b) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tremelimumab + durvalumab				
Tremelimumab	Single dose on day 1 in cycle 1	1	1	1.0
Durvalumab	1 x every 28 days	13	1	13.0
Best supportive care[3]	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care				
Best supportive care [3]	Different from patient to patient			

3 When comparing durvalumab in combination with tremelimumab versus best supportive care, the costs of best supportive care must also be additionally considered for the medicinal product assessed.

Consumption:

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).[4]

a) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tremelimumab + durvalumab					
Tremelimumab	300 mg	300 mg	1 x 300 mg	1.0	1 x 300 mg
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	13.0	39 x 500 mg
Appropriate comparator therapy					
Atezolizumab + bevacizumab					
Atezolizumab	1,200 mg	1,200 mg	1 x 1,200 mg	17.4	17.4 x 1,200 mg
	or				
	840 mg	840 mg	1 x 840 mg	26.1	26.1 x 840 mg
	or				
	1,680 mg	1,680 mg	2 x 840 mg	13.0	26 x 840 mg
Bevacizumab	15 mg/kg = 1,155 mg	1,155 mg	3 x 400 mg	17.4	52.2 x 400 mg

b) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tremelimumab + durvalumab					
Tremelimumab	300 mg	300 mg	1 x 300 mg	1.0	1 x 300 mg
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	13.0	39 x 500 mg

4 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Best supportive care[3]	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care					
Best supportive care[3]	Different 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 Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Tremelimumab + durvalumab					
Tremelimumab 300 mg	1 CIS	€ 27,320.89	€ 2.00	€ 2,669.16	€ 24,649.73
Durvalumab 500 mg	1 CIS	€ 2,167.38	€ 2.00	€ 206.55	€ 1,958.83
Appropriate comparator therapy					
Atezolizumab + bevacizumab					
Atezolizumab 1,200 mg	1 CIS	€ 4,129.23	€ 2.00	€ 398.62	€ 3,728.61
Atezolizumab 840 mg	1 CIS	€ 2,907.75	€ 2.00	€ 279.03	€ 2,626.72
Bevacizumab 25 mg/ml	1 CIS	€ 1,553.33	€ 2.00	€ 146.43	€ 1,404.90
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

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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 01.10.2009 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 the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation 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 purchase 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 of retail pharmacist services (Hilfstaxe).

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called indetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGBV.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product: "Imjudo in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC)."

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:

Product information for tremelimumab (Imjudo); product information for IMJUDO® 20 mg/ml concentrate for the preparation of an infusion solution; last revised: August 2023

b) Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product: "Imjudo in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC)."

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:

Product information for tremelimumab (Imjudo); product information for IMJUDO® 20 mg/ml concentrate for the preparation of an infusion solution; last revised: August 2023

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 25 January 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 17 January 2023.

On 30 March 2023, the pharmaceutical company submitted a dossier for the benefit assessment of tremelimumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 March 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 tremelimumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 June 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 July 2023. The deadline for submitting statements was 24 July 2023.

The oral hearing was held on 7 August 2023.

On 9 August 2023, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 8 August 2023 replaces version 1.0 of the dossier assessment dated 27 June 2023. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 26 September 2023, and the proposed resolution was approved.

At its session on 5 October 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 January 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	17 January 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	2 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 August 2023	Conduct of the oral hearing
Working group Section 35a	16 August 2023 6 September 2023 20 September 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	26 September 2023	Concluding discussion of the draft resolution
Plenum	5 October 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 5 October 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken