Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 5 October 2023, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. **In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Tremelimumab in accordance with the resolution of 5 October 2023 for the therapeutic indication: "for first-line treatment of metastatic NSCLC with no sensitising EGFR mutations or ALK-positive mutations":**

Tremelimumab

Resolution of: 5 October 2023
Entry into force on: 5 October 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 20 February 2023):

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 therapeutic indication according to marketing authorisation.

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

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

Appropriate comparator therapy:

– Atezolizumab in combination with bevacizumab

Extent and probability of the additional benefit of tremelimumab in combination with durvalumab compared to atezolizumab in combination with bevacizumab:

An additional benefit is not proven.

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

Appropriate comparator therapy:

– Best supportive care

Extent and probability of the additional benefit of tremelimumab in combination with durvalumab compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

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.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↔	No relevant difference for the benefit assessment.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: No data available.
n.a.: not assessable

Adjusted indirect comparison

Tremelimumab + durvalumab vs atezolizumab + bevacizumab via the bridge comparator sorafenib:

HIMALAYA study: Tremelimumab + durvalumab vs sorafenib; RCT

IMbrave150 study: Atezolizumab + bevacizumab vs sorafenib; RCT

1 Data from the dossier assessment of the IQWiG (A23-27, A23-30) unless otherwise indicated.

Mortality

Endpoint	Tremelimumab + durvalumab or atezolizumab + bevacizumab		Sorafenib		Group difference
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Overall survival					
Tremelimumab + durvalumab vs sorafenib					
HIMALAYA (data cut-off from 27.08.2021)	393	16.4 [14.2; 19.6] *262 (66.7)*	389	13.8 [12.3; 16.1] *293 (75.3)*	0.78 [0.66; 0.92] 0.004 AD: 2.6 months
Atezolizumab + bevacizumab vs sorafenib					
IMbrave150 (data cut-off from 31.08.2020)	375	19.4 [17.1; 23.7] *196 (52.3)*	183	13.4 [11.4; 16.9] *110 (60.1)*	0.66 [0.52; 0.83] < 0.001 AD: 6 months
Indirect comparison via bridge comparators[b]:					
Tremelimumab + durvalumab vs atezolizumab + bevacizumab					1.18 [0.89; 1.57] 0.246

Morbidity

Endpoint	Tremelimumab + durvalumab or atezolizumab + bevacizumab		Sorafenib		Group difference
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value
Symptomatology (EORTC QLQ-C30, EORTC QLQ-HCC 18)					
No suitable data[c]					
Health status (EQ-5D VAS, PGIC)					
No suitable data[c]					

Health-related quality of life

Endpoint	Tremelimumab + durvalumab or atezolizumab + bevacizumab		Sorafenib		Group difference
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value
(EORTC QLQ-C30, EORTC QLQ-HCC18)					
No suitable data[c]					

Side effects[d]

Endpoint	Tremelimumab + durvalumab or atezolizumab + bevacizumab		Sorafenib		Group difference
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
Tremelimumab + durvalumab vs sorafenib					
HIMALAYA	388	0.5 [0.5; 0.6] *378 (97.4)*	374	0.3 [0.3; 0.4] *357 (95.5)*	-
Atezolizumab + bevacizumab vs sorafenib					
IMbrave150	368	n.d. *361 (98.1)*	174	n.d. *171 (98.3)*	-
Serious adverse events (SAE)					
Tremelimumab + durvalumab vs sorafenib					
HIMALAYA	388	20.4 [14.1; 33.0] *157 (40.5)*	374	31.2 [23.8; n.c.] *111 (29.7)*	1.30 [1.02; 1.66] 0.034
Atezolizumab + bevacizumab vs sorafenib					
IMbrave150	368	n.d. *146 (39.7)*	174	n.d. *52 (29.9)*	1.10 [0.80; 1.51] 0.570

Endpoint	Tremelimumab + durvalumab or atezolizumab + bevacizumab		Sorafenib		Group difference
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Indirect comparison via bridge comparators:					
Tremelimumab + durvalumab vs atezolizumab + bevacizumab					1.18 [0.79; 1.76]
Severe adverse events (CTCAE grade ≥ 3)					
Tremelimumab + durvalumab vs sorafenib					
HIMALAYA	388	7.4 [5.7; 11.1] *211 (54.4)*	374	4.5 [2.8; 6.1] *210 (56.1)*	0.80 [0.66; 0.97] 0.022 AD: 2.9 months
Atezolizumab + bevacizumab vs sorafenib					
IMbrave150	368	n.d. *236 (64.1)*	174	n.d. *104 (59.8)*	0.80 [0.63; 1.01] 0.065
Indirect comparison via bridge comparators:					
Tremelimumab + durvalumab vs atezolizumab + bevacizumab					1.00 [0.74; 1.35]
Discontinuation due to AEs					
Tremelimumab + durvalumab vs sorafenib					
HIMALAYA	388	n.r. *53 (13.7)*	374	n.r. *63 (16.8)*	0.74 [0.51; 1.06] 0.099
Atezolizumab + bevacizumab vs sorafenib					
IMbrave150	368	n.d. *62 (16.8)*	174	n.d. *19 (10.9)*	1.06 [0.63; 1.79] 0.815
Indirect comparison via bridge comparators:					
Tremelimumab + durvalumab vs atezolizumab + bevacizumab					–[e]
Specific adverse events					
PRO-CTCAE				No suitable data[f]	

Endpoint	Tremelimumab + durvalumab or atezolizumab + bevacizumab		Sorafenib		Group difference
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Immune-mediated AEs				No suitable data[g]	
Bleeding (AEs, SAEs, severe AEs)				No suitable data[g]	

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Indirect comparison according to Bucher
[c] No analyses of first-time deterioration are available for the HIMALAYA study.
[d] For endpoints in the side effects category, the data cut-off from 27.08.2021 was used for the HIMALAYA study and the data cut-off from 29.11.2019 was used for the IMbrave150 study.
[e] No indirect comparison is calculated as the requirement for the certainty of results to perform an adjusted indirect comparison is not met.
[f] Only collected in the HIMALAYA study
[g] There are no data in Module 4 A

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PGIC = Patient Global Impression of Change; PRO = Patient-reported Outcome; QLQ-C30 = Quality of Life Questionnaire Cancer-30; QLQ-HCC18 = HCC-specific Quality of Life Questionnaire; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

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

No data available.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
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↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: No data available.
n.a.: not assessable

2. Number of patients or demarcation of patient groups eligible for treatment

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

Approx. 1,300 to 3,770 patients

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

Approx. 410 to 1,200 patients

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: 21 September 2023):

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

Treatment with tremelimumab 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.

4. Treatment costs

Annual treatment costs:

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

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Tremelimumab + durvalumab	
Tremelimumab	€ 24,649.73
Durvalumab	€ 76,394.37
Total	€ 101,044.10
Appropriate comparator therapy:	
atezolizumab + bevacizumab	
Atezolizumab	€ 64,877.81 - € 68,557.39
Bevacizumab	€ 73,335.78
Total	€ 138,213.59 - € 141,893.17

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2023

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Tremelimumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	1.0	€ 100
Durvalumab		€ 100	1	13.0	€ 1,300
Atezolizumab		€ 100	1	13.0 - 26.1	€ 1,300 - € 2,610
Bevacizumab		€ 100	1	17.4	€ 1,740

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Tremelimumab + durvalumab	
Tremelimumab	€ 24,649.73
Durvalumab	€ 76,394.37
Total	€ 101,044.10
Best supportive care [2]	Different from patient to patient
Appropriate comparator therapy:	
Best supportive care	
Best supportive care[2]	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2023

Costs for additionally required SHI services: not applicable

2 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.

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Tremelimumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	1.0	€ 100
Durvalumab		€ 100	1	13.0	€ 1,300

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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

The following medicinal products with new active ingredients that can be used in a combination therapy with tremelimumab in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

– Durvalumab (Imfinzi)

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

The following medicinal products with new active ingredients that can be used in a combination therapy with durvalumab in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

– Durvalumab (Imfinzi)

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

II. In Annex XIIa of the Pharmaceuticals Directive, the following information shall be added in alphabetical order:

"Active ingredient of the assessed medicinal product

Tremelimumab

Resolution according to Section 35a paragraph 3 SGB V from

5 October 2023

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

Patient group a

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

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names)

Durvalumab (Imfinzi)

Period of validity of the designation (since... or from... to)

Since 5 October 2023

Patient group b

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

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names)

Durvalumab (Imfinzi)

Period of validity of the designation (since... or from... to)

Since 5 October 2023"

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 5 October 2023.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 5 October 2023

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

Prof. Hecken