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)
Durvalumab (new therapeutic indication: hepatocellular carcinoma, first-line, monotherapy)

of 6 June 2024

At its session on 6 June 2024, 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 Durvalumab in accordance with the resolution of 5 October 2023 on the therapeutic indication "for the first-line treatment of advanced or unresectable hepatocellular carcinoma":

Durvalumab

Resolution of: 6 June 2024
Entry into force on: 6 June 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 15 November 2023):

IMFINZI as monotherapy is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

Therapeutic indication of the resolution (resolution of 6 June 2024):

See new 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

  or

- durvalumab in combination with tremelimumab

Extent and probability of the additional benefit of 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 durvalumab compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

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

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

<u>Adjusted indirect comparison</u>
Durvalumab vs atezolizumab + bevacizumab via the bridge comparator sorafenib:

HIMALAYA study: durvalumab vs sorafenib; RCT

IMbrave150 study: atezolizumab + bevacizumab vs sorafenib; RCT

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A23-138) unless otherwise indicated.

Mortality

Endpoint	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					
Durvalumab vs sorafenib					
HIMALAYA (data cut-off from 27.08.2021)	389	16.6 [14.1; 19.1] *280 (72.0)*	389	13.8 [12.3; 16.1] *293 (75.3)*	0.86 [0.73; 1.01] 0.068[b]
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[c] AD: 6 months
Indirect comparison via bridge comparators[d]:					
Durvalumab vs atezolizumab + bevacizumab					1.30 [0.98; 1.72] 0.064

Morbidity

Endpoint	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[e]					
Health status (EQ-5D VAS, PGIC)					
No suitable data[e]					

Health-related quality of life

Endpoint	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[e]					

Side effects[f]

Endpoint	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)					
Durvalumab vs sorafenib					
HIMALAYA	388	1.0 [0.9; 1.1] *345 (88.9)*	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)					
Durvalumab vs sorafenib					
HIMALAYA	388	n.r. [n.c.; n.c.] *115 (29.6)*	374	31.2 [23.8; n.c.] *111 (29.7)*	0.91 [0.70; 1.18] 0.463[g]
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[g]

Endpoint	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:					
Durvalumab vs atezolizumab + bevacizumab					0.83 [0.55; 1.25] 0.364
Severe adverse events (CTCAE grade ≥ 3)					
Durvalumab vs sorafenib					
HIMALAYA	388	16.3 [11.1; n.c.] *158 (40.7)*	374	4.5 [2.8; 6.1] *210 (56.1)*	0.54 [0.44; 0.67] < 0.001[g] AD: 11.8 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[g]
Indirect comparison via bridge comparators:					
Durvalumab vs atezolizumab + bevacizumab					0.68 [0.49; 0.93] 0.015
Discontinuation due to AEs					
Durvalumab vs sorafenib					
HIMALAYA	388	n.r. [n.c.; n.c.] *32 (8.2)*	374	n.r. *63 (16.8)*	0.45 [0.29; 0.68] < 0.001[g]
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[g]
Indirect comparison via bridge comparators:					
Durvalumab + tremelimumab vs atezolizumab + bevacizumab					–[h]
Specific adverse events					

Endpoint	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]
PRO-CTCAE					No suitable data[i]
Immune-mediated AEs					No suitable data[j]
Bleeding (AEs, SAEs, severe AEs)					No suitable data[j]

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] HR and 95% CI from a Cox proportional hazards model, stratified by aetiology of liver disease [hepatitis B vs hepatitis C vs other], ECOG-PS [0 vs 1], macrovascular invasion [yes vs no]); p value from stratified log-rank test
[c] HR and 95% CI from a Cox proportional hazards model, stratified by geographic region (Asia excluding Japan / Rest), extrahepatic spread and/or macrovascular invasion (yes / no) and AFP at screening (< 400 ng/ml / ≥ 400 ng/ml); p value from stratified log-rank test
[d] Indirect comparison according to Bucher
[e] No analyses of first-time deterioration are available for the HIMALAYA study.
[f] 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.
[g] Effect estimate and 95% CI from an unstratified Cox proportional hazards model; p value from unstratified log-rank test.
[h] No indirect comparison is calculated as the requirement for the reliability of data to perform an adjusted indirect comparison is not met.
[i] Only collected in the HIMALAYA study
[j] There are no data in Module 4 A

Abbreviations used:
AD = absolute difference; AFP = alpha-fetoprotein; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HCC = hepatocellular carcinoma; 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) <u>Adults with advanced or unresectable hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy</u>

An additional benefit is not proven.

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
↓: statistically significant and relevant negative effect with low/unclear reliability of data
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↓↓: 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. 1,440 to 4,150 patients

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

Approx. 460 to 1,320 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 Imfinzi (active ingredient: durvalumab) at the following publicly accessible link (last access: 28 May 2024):

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

Treatment 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.

4. Treatment costs

Annual treatment costs:

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:	
Durvalumab	€ 79,750.71
Appropriate comparator therapy:	
atezolizumab + bevacizumab	
Atezolizumab	€ 67,767.78 - € 71,591.78
Bevacizumab	€ 76,520.50
Total	€ 144,288.28 - € 148,112.28
Durvalumab + tremelimumab	
Durvalumab	€ 79,750.71
Tremelimumab	€ 25,761.88
Total	€ 105,512.59

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2024)

Costs for additionally required SHI services: not applicable

Other SHI benefits:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient year	Costs/ patient year
Medicinal product to be assessed:					
Durvalumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	13.0	€ 1,300
Appropriate comparator therapy:					

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

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Durvalumab	€ 79,750.71
Best supportive care[2]	Different from patient to patient
Appropriate comparator therapy:	

[2] When comparing durvalumab with best supportive care, the costs of best supportive care must also be additionally considered for the medicinal product to be assessed.

Designation of the therapy	Annual treatment costs/ patient
Best supportive care[2]	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2024)

Costs for additionally required SHI services: not applicable

Other SHI benefits:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient year	Costs/ patient year
Medicinal product to be assessed:					
Durvalumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 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

– No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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

– No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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. Entry into force

1. **The resolution will enter into force on the day of its publication on the website of the G-BA on 6 June 2024.**

2. **The period of validity of the resolution is limited to 1 January 2025.**

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

Berlin, 6 June 2024

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

Prof. Hecken