Durvalumab (new therapeutic indication: hepatocellular carcinoma, first-line, combination with tremelimumab)

Resolution of: 5 October 2023/ 8 October 2024 valid until: unlimited
Entry into force on: 5 October 2023/ 8 October 2024
Federal Gazette, BAnz AT 20 11 2023 B3/ BAnz AT 24 10 2024 B3

New therapeutic indication (according to the marketing authorisation of 30 January 2023):

Imfinzi in combination with tremelimumab 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 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

Extent and probability of the additional benefit of durvalumab in combination with tremelimumab 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 in combination with tremelimumab 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

Durvalumab + tremelimumab vs atezolizumab + bevacizumab via the bridge comparator sorafenib:

HIMALAYA study: durvalumab + tremelimumab 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	Durvalumab + tremelimumab 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 + tremelimumab 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]:					
Durvalumab + tremelimumab vs atezolizumab + bevacizumab					1.18 [0.89; 1.57] 0.246

Morbidity

Endpoint	Durvalumab + tremelimumab 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	**Durvalumab + tremelimumab 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	Durvalumab + tremelimumab 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 + tremelimumab 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)					
Durvalumab + tremelimumab 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
Indirect comparison via bridge comparators:					
Durvalumab + tremelimumab vs atezolizumab + bevacizumab					1.18 [0.79; 1.76]
Severe adverse events (CTCAE grade ≥ 3)					
Durvalumab + tremelimumab 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

Endpoint	Durvalumab + tremelimumab 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 + tremelimumab vs atezolizumab + bevacizumab					1.00 [0.74; 1.35]
Discontinuation due to AEs					
Durvalumab + tremelimumab 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:					
Durvalumab + tremelimumab vs atezolizumab + bevacizumab					–[e]
Specific adverse events					
PRO-CTCAE				No suitable data[f]	
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:

Endpoint	Durvalumab + tremelimumab 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]
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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∅: 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: 21 September 2023):

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:

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:	
Durvalumab + tremelimumab	
Durvalumab	€ 76,394.37
Tremelimumab	€ 24,649.73
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
Durvalumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	13.0	€ 1,300
Tremelimumab		€ 100	1	1.0	€ 100
Atezolizumab		€ 100	1	13.0 - 26.1	€ 1,300 - € 2,610
Bevacizumab		€ 100	1	17.4	€ 1,740

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 + tremelimumab	
Durvalumab	€ 76,394.37
Tremelimumab	€ 24,649.73
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

Other SHI services:

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

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.

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 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:

- Tremelimumab (Imjudo)

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:

- Tremelimumab (Imjudo)

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.