Resolution

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Atezolizumab (new therapeutic indication: hepatocellular carcinoma, combination with bevacizumab)

of 20 May 2021

At its session on 20 May 2021, 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 on DD Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Atezolizumab in accordance with the resolution of 4. April 2020:

Atezolizumab

Resolution of: 20 May 2021
Entry into force on: 20 May 2021
BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 27 October 2020):

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

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

see new therapeutic indication according to marketing authorisation

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

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

Appropriate comparator therapy for atezolizumab in combination with bevacizumab:

- Sorafenib or lenvatinib

Extent and probability of the additional benefit of Atezolizumab in combination with bevacizumab compared to sorafenib:

Indication of a considerable additional benefit

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

Appropriate comparator therapy for Atezolizumab in combination with bevacizumab:

- Best supportive care

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

An additional benefit is not proven.

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival; In the subgroup analysis, there is an effect modification depending on whether there is a viral or non-viral aetiology of HCC: for the patients with viral aetiology, there is an advantage in overall survival, while for the patients with non-viral aetiology, there is no advantage in overall survival.
Morbidity	↑↑	Advantages in many symptomatic endpoints and in the endpoint Health status
Health-related quality of life	↑↑	Benefits in the endpoints of Body image, Nutrition, Role function, Physical, Emotional, Cognitive, Social function
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
∅: There is no usable data for the benefit assessment.
n.a.: not assessable

[1] Data from the dossier evaluation of the IQWiG (A20-97) and from the addendum (A20-97), unless otherwise indicated.

IMbrave150 study: Atezolizumab + bevacizumab **vs** sorafenib

Study design: open randomised controlled phase III study

Mortality

Endpoint	**Atezolizumab + Bevacizumab**		**Sorafenib**		Intervention vs control
	N	Median time to event in months [95 % CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Overall survival (data cut-off of 31/8/2020)					
Total population[p]	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: 6.0 months
Subgroups according to aetiology of HCC					
Hepatitis B	200	19,1 [16.3; n.c.] 86 (52.4)	91	12,7 [7.4; 16.9] 54 (59.3)	0,58 [0.42; 0.13] 0,001 AD: 6.4 months
Hepatitis C	72	24,6 [19.8; n.c.] 31 (43.1)	37	13,1 [7.4; 20.4] 24 (64.9)	0,43 [0.25; 0.73] 0,002 AD: 11.5 months
Viral (hepatitis B or C)					0,53 [0.40; 0.71][d] < 0.001[d]
non-viral	103	17,0 [11.3; 22.8] 65 (63.1)	55	15.7 [11.4; 26.4] 32 (58.2)	1.01 [0.66; 1.54] (0.943)[e]
					Interaction: 0.035[o]

Morbidity

Endpoint	Atezolizumab + Bevacizumab		Sorafenib		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Progression-free survival[n] (data cut-off 29/8/2019)					
Global cohort[b]	336	6.8 [5.8; 8.3] 197 (58.6)	165	4.3 [4.0; 5.6] 109 (66.1)	0.59 [0.47; 0.76] < 0.0001 AD: 2.5 months
Symptomatology (EORTC QLQ-C30 - Symptom scales[f] (data cut-off from 29/8/2019))					
Fatigue	375	2.10 [1.48; 2.20] 253 (67.5)	183	1.45 [1.08; 1.51] 129 (70.5)	0.71 [0.57; 0.89] 0.002[c] AD: 0.65 months
Nausea and vomiting	375	14.29 [8.31; n.b.] 144 (38.4)	183	4.60 [3.48; 5.62] 88 (48.1)	0.49 [0.37; 0.64] <0.001[c] AD: 9.69 months
Pain	375	3.48 [2.79; 4.27] 234 (62.4)	183	1.58 [1.31; 2.33] 119 (65.0)	0.62 [0.49; 0.79] <0.001[c] AD: 1.9 months
Dyspnoea	375	9.66 [6.67; 11.93] 162 (43.2)	183	4.17 [2.27; 5.32] 91 (49.7)	0.59 [0.45; 0.78] <0.001[c] AD: 5.49 months
Insomnia	375	7.16 [5.55; 9.43] 175 (46.7)	183	4.86 [3.48; 6.97] 80 (43.7)	0.79 [0.60; 1.04] 0.096[c]
Loss of appetite	375	6.28 [4.76; 8.51] 197 (52.5)	183	3.02 [2.14; 3.98] 108 (59.0)	0.57 [0.45; 0.73] <0.001[c] AD: 3.18 months
Constipation	375	11.30 [9.69; n.b.] 140 (37.3)	183	4.17 [2.76; 6.08] 83 (45.4)	0.48 [0.36; 0.64] <0.001[c] AD: 7.13 months
Diarrhoea	375	10.71 [7.98; n.b.] 148 (39.5)	183	2.83 [2.10; 3.52] 103 (56.3)	0.34 [0.26; 0.44] <0.001[c] AD: 7.88 months

Endpoint	Atezolizumab + Bevacizumab		Sorafenib		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Symptomatology (EORTC QLQ-HCC18 - Symptom scales[f] (data cut-off from 29/8/2019))					
Fatigue	375	2.33 [2.07; 3.52] 238 (63.5)	183	1.41 [0.85; 1.58] 126 (68.9)	0.64 [0.51; 0.81] <0.001[c] AD: 0.92 months
Icterus	375	4.21 [3.52; 5.55] 203 (54.1)	183	2.14 [1.58; 3.48] 103 (56.3)	0.66 [0.52; 0.85] 0.001[c] AD: 2.07 months
Pain	375	4.83 [3.84; 5.59] 205 (54.7)	183	3.45 [2.10; 4.86] 98 (53.6)	0.71 [0.55; 0.91] 0.006[c] AD: 1.38 months
Fever	375	5.55 [3.91; 7.75] 192 (51.2)	183	4.17 [3.02; 7.29] 86 (47.0)	0.87 [0.67; 1.13] 0.297[c]
Abdominal swelling	375	9.69 [7.62; 11.04] 159 (42.4)	183	5.52 [3.29; n.c.] 69 (37.7)	0.61 [0.46; 0.82] 0.001[c] AD: 4.17 months
Health Status[g] (EQ-5D VAS (data cut-off of 29/8/2019))					
≥ 10 points	375	4.21 [3.52; 6.21] 213 (56.8)	183	1.64 [1.45; 3.02] 115 (62.8)	0.57 [0.45; 0.872] <0.001[c] AD: 2.57 months
≥ 15 points	336	9.8 [7.1; n.b.] 144 (42.9)	165	3.5 [2.8; 5.1] 87 (52.7)	0.53 [0.40; 0.70] <0.001[c] AD: 6.3 months

(continuation)

Health-related quality of life

Endpoint	Atezolizumab + Bevacizumab		Sorafenib		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
EORTC QLQ-C30 - Functional Scales[g] (data cut-off from 29/8/2019)					
global health status	375	3.52 [2.73; 4.21] 222 (59.2)	183	1.48 [1.38; 2.17] 119 (65.0)	0.62 [0.49; 0.78] <0.001[c] AD: 2.04 months
Physical function	375	4.53 [3.58; 6.24] 212 (56.5)	183	2.10 [1.48; 3.48] 111 (60.7)	0.63 [0.50; 0.81] <0.001[c] AD: 2.43 months
Role function	375	4.17 [3.12; 4.86] 222 (59.2)	183	1.61 [1.41; 2.14] 126 (68.9)	0.60 [0.47; 0.75] <0.001[c] AD: 2.56 months
Emotional function	375	n.a. [11.70; n.c.] 129 (34.4)	183	4.86 [2.86; 7.06] 90 (49.2)	0.45 [0.34; 0.59] <0.001[c]
Cognitive function	375	4.57 [3.48; 9.00] 195 (52.0)	183	2.83 [1.87; 4.17] 102 (55.7)	0.66 [0.52; 0.85] 0.002[c] AD: 1.74 months
Social function	375	3.61 [2.79; 4.57] 222 (59.2)	183	2.10 [1.48; 2.83] 116 (63.4)	0.64 [0.50; 0.80] <0.001[c] AD: 1.51 months
EORTC QLQ-HCC18 - Functional Scales[f] (data cut-off of 29/8/2019)					
Body image	375	3.58 [2.83; 4.90] 227 (60.5)	183	2.53 [1.84; 3.61] 104 (56.8)	0.79 [0.62; 1.00] 0.0495[c] AD: 1.05 months
Nutrition	375	5.65 [4.21; 7.16] 197 (52.5)	183	2.17 [1.61; 3.02] 117 (63.9)	0.49 [0.39; 0.62] <0.001[c] AD: 3.48 months
Sex life	375	n.a. [10.15; n.c.] 142 (37.9)	183	6.74 [5.49; n.c.] 63 (34.4)	0.85 [0.63; 1.15] 0.286[c]

(continuation)

Side effects (29/11/2019 data cut-off (global cohort) and 29/8/2019 data cut-off (cohort in China))

Endpoint	Atezolizumab + Bevacizumab		Sorafenib		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	368	n. d. 361 (98.1)	174	n. d. 171 (98.3)	-
Serious adverse events (SAE)					
	368	n. d. 146 (39.7)	174	n. d. 52 (29.9)	1.10 [0.80; 1.51] 0.570[h]
Severe adverse events (CTCAE grade 3 or 4)					
	368	n. d. 236 (64.1)	174	n. d. 104 (59.8)	0.80 [0.63; 1.01] 0.065[h]
Therapy discontinuation because of adverse events[i]					
	368	n. d. 62 (16.8)	174	n. d. 19 (10.9)	1.06 [0.63; 1.79] 0.815[h]
Specific adverse events					
Immune-mediated AEs (AEs, SAEs, severe AEs)	no usable data available[j,k]				
Bleeding (AEs)	368	n. d. 97 (26.4)	174	n. d. 32 (18.4)	1.16 [0.78; 1.73] 0.473[h]
Haemorrhages (SAEs)	368	n. d. 36 (9.8)	174	n. d. 15 (8.6)	0.76 [0.41; 1.40] 0.382[h]
Bleeding (severe AEs)	368	n. d. 31 (8.4)	174	n. d. 12 (6.9)	0.86 [0.44; 1.68] 0.652[h]
Hand-foot syndrome[l] (PT, severe AEs)	368	n. d. 0 (0)	174	n. d. 15 (8.6)	-[m];< 0.001[h]
Alopecia (PT, AE)	368	n. d. 4 (1.1)	174	n. d. 24 (13.8)	0.06 [0.02; 0.17] < 0.001[h]
Endpoint	**Atezolizumab + Bevacizumab**		**Sorafenib**		Intervention vs

					control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Diarrhoea (PT, severe AEs)	368	n. d. 9 (2.4)	174	n. d. 9 (5.2)	0.35 [0.14; 0.90] 0.023[h]
General disorders and administration site conditions (SOC, severe AEs)	368	n. d. 18 (4.9)	174	n. d. 15 (8.6)	0.42 [0.21; 0.82] 0.009[h]
Bilirubin elevated in the blood (PT, severe AEs)	368	n. d. 12 (3.3)	174	n. d. 10 (5.7)	0.42 [0.18; 0.99] 0.041[h]
Metabolic and nutritional disorders (SOC, severe AEs)	368	n. d. 35 (9.5)	174	n. d. 21 (12.1)	0.56 [0.33; 0.94] 0.028[h]
Respiratory, thoracic and mediastinal disorders (SOC, severe SAEs)	368	n. d. 15 (4.1)	174	n. d. 7 (4.0)	0.44 [0.20; 0.99] 0.041[h]
Infections and infestations	368	n. d. 26 (7.1)	174	n. d. 3 (1.7)	3.60 [1.10; 11.83] 0.024[h]

[A] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] This includes 137 patients who are also included in the cohort in China.
[c] Effect estimate 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 via stratified log-rank test
[d] own calculation of the meta-analysis
[e] effect estimate and 95% CI from a Cox-Proportional-Hazards-Model; p-value via log-rank test
[f] Time to first deterioration; defined as an increase in score of at least 10 points from baseline
[g] Time to first deterioration; defined as a decrease in score of at least 10 points from baseline.
[h] Effect estimate and 95% CI from an unstratified Cox-Proportional-Hazards-Model; p-value via unstratified log-rank test
[i] AEs that resulted in the discontinuation of at least one active ingredient component were counted as events.
[j] It is unclear which operationalisations are behind the AESIs submitted by the company.
[k] The pharmaceutical company did not provide aggregated analyses of immune-mediated AEs, but only individual immune-mediated AEs evaluated in the AESI.
[l] PT Palmar-plantar erythrodysesthesia syndrome of the MedDRA
[m] Effect estimate and 95% CI cannot be interpreted meaningfully
[n] Information from the dossier of the pharmaceutical company
[o] p-value for the pharmaceutical company interaction test according to the original classification of the subgroups
[p] 501 patients in the global cohort + 57 patients in the Chinese cohort who are not in the global cohort at the same time

Abbreviations used:
AESI: adverse events of special interest; AFP: Alpha-fetoprotein; AD: Absolute difference: CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European organisation for Research and Treatment of Cancer; HCC: hepatocellular carcinoma; HR: hazard ratio; n. d.: no data; CI: Confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; n: Number of patients evaluated; n: Number of patients with (at least 1) event; n. c. = not calculable; n.a. = not achieved; PT QLQ-C30: Quality of Life Questionnaire–Cancer -30; QLQ-HCC18: HCC-specific Quality of Life Questionnaire; RCT: randomised controlled study; SOC: System Organ Class; SAE: serious adverse event; AE: adverse event; vs: versus.

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

No adequate data are available to allow an assessment of the additional benefit.

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
↓: 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
∅: There is no usable data for the benefit assessment.
n.a.: not assessable

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

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

approx. 1,300 to 3770 patients

b) Adult patients with advanced HCC with Child-Pugh B without previous systemic 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 Tecentriq (active ingredient: atezolizumab) at the following publicly accessible link (last access: 27 January 2021):

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

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

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on atezolizumab:

- training material for health professionals
- Patient pass.

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

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

4. Treatment costs

Annual treatment costs:

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

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Atezolizumab	€ 67,766.91
Bevacizumab	€ 76,518.41
Total:	€ 144,285.32
Appropriate comparator therapy:	

Name of therapy	Annual treatment costs/patient
Lenvatinib	€ 56,024.22
Sorafenib	€ 59,931.83

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 1 May 2021).

Costs for additionally required SHI services: not applicable

Other SHI services:

Name of 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	€ 71	1	17.4	€ 1,235.40
Bevacizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17.4	€ 1,235.40

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

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Atezolizumab	€ 67,766.91
Bevacizumab	€ 76,518.41
Total:	€ 144,285.32
Best supportive care	varies from patient to patient
Appropriate comparator therapy:	

Name of therapy	Annual treatment costs/patient
Best supportive care	varies from patient to patient

costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 1 May 2021).

Costs for additionally required SHI services: not applicable

Other SHI services:

Name of 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	€ 71	1	17.4	€ 1,235.40
Bevacizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17.4	€ 1,235.40

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 20 May 2021.

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

Berlin, 20 May 2021

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

Prof. Hecken