Resolution

Gemeinsamer Bundesausschuss

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: Breast Cancer, Triple Negative, PD-L1 Expression ≥ 1%)

of 2 April 2020

On 2 April 2020, the Federal Joint Committee (G-BA) resolved by written statement to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 20 June 2019:

Atezolizumab

Resolution of: 2 April 2020
Entry into force on: 2 April 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 26 August 2019):

Tecentriq in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

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

Adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease

Appropriate comparator therapy:

A systemic therapy containing anthracycline and/or taxane, taking into account the marketing authorisation of the medicinal products.

Extent and probability of the additional benefit of atezolizumab in combination with nab-paclitaxel compared with the appropriate comparator therapy:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

Adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease

Study IMpassion130:

Atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel

Sub-population: Patients whose tumours have a PD-L1 expression ≥ 1% of tumour infiltrating immune cells

[1] Data from the dossier evaluation of the IQWiG (A19-81) and the addendum (A20-11) unless otherwise indicated.

Mortality

Endpoint	Atezolizumab + nab-paclitaxel		Placebo + nab-paclitaxel		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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	185	25.0 [19.6; 30.7] *94 (50.8)*	184	18.0 [13.6; 20.1] *110 (59.8)*	0.71 [0.54; 0.93] 0.013 + 7.0 months

Morbidity

Progression-free survival (PFS)[b]					
	149	7.5 [6.7; 9.2] *149 (80.5)*	163	5.3 [3.8; 5.6] *163 (88.6)*	0.63 [0.50; 0.80] < 0.0001 + 2.2 months
Symptomatology					
EORTC QLQ-C30 (symptom scales) [c,d]					
Fatigue	164	1.8 [1.1; 1.9] *142 (86.6)*	158	1.9 [1.1; 2.7] *126 (79.7)*	1.06 [0.83; 1.35] 0.613
Nausea and vomiting	164	3.8 [2.8; 6.0] *115 (70.1)*	158	4.3 [2.8; 5.6] *102 (64.6)*	1.01 [0.77; 1.33] 0.934
Pain	164	3.1 [2.0; 4.6] *123 (75.0)*	158	5.1 [3.5; 7.4] *100 (63.3)*	1.34 [1.03; 1.76] 0.031
Dyspnoea	164	3.9 [3.2; 5.6] *103 (62.8)*	158	4.8 [2.9; 7.4] *90 (57.0)*	1.03 [0.78; 1.37] 0.821
Insomnia	164	6.6 [4.4; 12.2] *90 (54.9)*	158	7.3 [4.0; 15.6] *76 (48.1)*	1.03 [0.75; 1.39] 0.863
Loss of appetite	164	4.9 [3.8; 8.4] *97 (59.1)*	158	4.3 [3.5; 6.1] *93 (58.9)*	0.94 [0.70; 1.25] 0.661

Constipation	164	4.8 [3.7; 7.8] *102 (62.2)*	158	5.7 [3.4; 7.6] *93 (58.9)*	0.95 [0.72; 1.26] 0.744
Diarrhoea	164	4.9 [3.7; 8.3] *100 (61.0)*	158	6.0 [4.7; 9.3] *87 (55.1)*	1.12 [0.84; 1.49] 0.432
EORTC QLQ-BR23 (symptom scales) [c,d]					
Side effects of the systemic therapy	164	1.1 [1.0; 1.2] *139 (84.8)*	158	1.9 [1.1; 1.9] *124 (78.5)*	1.18 [0.92; 1.51] 0.205
Symptoms in the breast area	164	17.4 [9.8; 24.8] *67 (40.9)*	158	12.0 [8.2; n.a.] *60 (38.0)*	0.96 [0.67; 1.37] 0.813
Symptoms in the arm area	164	4.6 [2.8; 5.6] *103 (62.8)*	158	4.1 2.8; 7.4] *93 (58.9)*	0.99 [0.75; 1.31] 0.945
Burden of hair loss	No usable data[e]				
Health status (EQ-5D VAS)[c,f]					
	161	2.8 [1.9; 3.7] *122 (75.8)*	151	3.7 [2.8; 5.2] *102 (67.5)*	1.07 [0.82; 1.40] 0.590

Health-related quality of life

EORTC QLQ-C30 (functional scales) [c,f]					
Global health status	164	2.9 [2.1; 3.7] *121 (73.8)*	158	2.8 [2.4; 3.8] *104 (65.8)*	1.00 [0.77; 1.31] 0.982
Role function	164	2.8 [1.9; 3.7] *122 (74.4)*	158	2.8 [2.4; 3.8] *119 (75.3)*	0.91 [0.71; 1.18] 0.493
Physical function	164	3.1 2.5; 4.4] *120 (73.2)*	158	3.8 [3.1; 5.2] *116 (73.4)*	0.97 [0.75; 1.25] 0.798
Emotional function	164	6.5 [5.0; 9.5] *90 (54.9)*	158	6.0 [3.8; 9.6] *86 (54.4)*	0.91 [0.67; 1.22] 0.512
Cognitive function	164	3.0 [2.8; 3.9] *117 (71.3)*	158	3.5 [2.8; 4.4] *108 (68.4)*	0.96 [0.74; 1.26] 0.792

Social function	164	2.8 [2.1; 4.7] *120 (73.2)*	158	2.9 [2.8; 3.8] *110 (69.6)*	0.96 [0.74; 1.25] 0.793
EORTC QLQ-BR23 (functional scales) [c,f]					
Body image	164	n.a. 38 (23.2)	158	n.a. 29 (18.4)	1.19 [0.73; 1.93] 0.479
Future perspective	164	3.8 [2.7; 7.4] *93 (56.7)*	158	4.7 [2.8; 14.3] *78 (49.4)*	1.04 [0.77; 1.40] 0.777
Sexual activity	164	23.7 [14.7; n.a.] *56 (34.1)*	158	n.a. [12.0; n.a.] *54 (34.2)*	0.88 [0.60; 1.28] 0.495
Sexual pleasure	No usable data[e]				

Side effects

Endpoint	**Atezolizumab + nab-paclitaxel**		**Placebo + nab-paclitaxel**		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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Adverse events (AE, presented additionally)					
	185	no data available *185 (100.0)*	181	no data available *177 (97.8)*	-
Serious adverse events (SAE)					
	185	no data available *43 (23.2)*	181	no data available *31 (17.1)*	1.17 [0.74; 1.87] 0.501
Severe adverse events (CTCAE grade 3–4)					
	185	no data available *97 (52.4)*	181	no data available *73 (40.3)*	1.20 [0.89; 1.63] 0.234
Discontinuation because of AE					
	185	no data available *37 (20.0)*	181	no data available *13 (7.2)*	2.34 [1.24; 4.41] 0.007
Specific adverse events					
Immune mediated AE	185	no data available *107 (57.8)*	181	no data available *66 (36.5)*	1.63 [1.20; 2.22] 0.002

Immune mediated AE	185	no data available *3 (1.6)*	181	no data available *3 (1.7)*	0.80 [0.16; 3.96] 0.778
Immune mediated severe AE (CTCAE grade 3–4)	185	no data available *10 (5.4)*	181	no data available *7 (3.9)*	1.20 [0.46; 3.17] 0.710
Investigations (SOC, severe AE, CTCAE grade 3–4)	185	no data available *26 (14.1)*	181	no data available *11 (6.1)*	2.06 [1.02; 4.18] 0.041

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Information from the dossier of the pharmaceutical company data cut-off of 2 January 2019
[c] Results for all patients for whom there was 1 evaluation at the start of study and at least 1 evaluation after the start of study.
[d] Time to first deterioration; defined as an increase of the score by ≥ 10 points compared with baseline
[e] Unclear proportion of patients with missing values at the start of study and during the course of the study
[f] Time to first deterioration; defined as a decrease of the score by ≥ 10 points compared with baseline

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HLT: high level term; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; MedDRA: Medical Dictionary for Regulatory Activities; n = number of patients with (at least one) event; n.a. = not achieved; PT: preferred term; QLQ-BR23: Quality of Life Questionnaire – Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire – Core 30; SMQ: standardised MedDRA questionnaire; SOC: system organ class; VAS: visual analogue scale; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	**Direction of effect/ Risk of bias**	**Summary**
Mortality	↑	Advantage in overall survival
Morbidity	↓	Disadvantage in the symptom scale pain
Health-related quality of life	↔	no relevant difference
Side effects	↓	Disadvantage in discontinuation because of AE and in specific AE

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

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

Adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease

approx. 920–1110 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: 11 February 2020):

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

Treatment with atezolizumab may only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gynaecology and obstetrics, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with breast cancer.

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 includes, in particular, instructions on how to deal with the immune mediated side effects potentially occurring under atezolizumab treatment as well as infusion-related reactions.

4. Treatment costs

Annual treatment costs:

Adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Atezolizumab	€ 80,979.34
nab-paclitaxel	€ 29,203.98
Total:	€ 110,183.32
Appropriate comparator therapy:	

Designation of the therapy	Annual treatment costs/patient
A therapy containing anthracycline and/or taxane	€ 2,081.55 – 56,917.24[2]

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2020

Costs for additionally required SHI services:

Designation of the therapy	Annual treatment costs/patient
Appropriate comparator therapy:	
Paclitaxel	€ 230.54

Other services covered by SHI funds:

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	€ 71	2	26	€ 1,846
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	39	€ 3,159
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Doxorubicin (monotherapy)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	5–11	€ 405 – 891
Doxorubicin (in combination with docetaxel or paclitaxel)	Surcharge for production of a parenteral preparation	€ 81	1	9–11	€ 729 – 891

2 The cost range results from the low-cost therapy doxorubicin and the cost-intensive therapy liposomal doxorubicin + cyclophosphamide

	containing cytostatic agents				
Doxorubicin (in combination with cyclophosphamide)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	7–9	€ 567 – 729
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Doxorubicin (pegylated, liposomal)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	13	€ 1,053
Liposomal doxorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Epirubicin (monotherapy)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	10–16	€ 810 – 1,296
Epirubicin (in combination with cyclophosphamide)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	12–16	€ 972 – 1,296
Epirubicin (in combination with paclitaxel)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	15–16	€ 1,215 – 1,296

Epirubicin (in combination with docetaxel)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	12–13	€ 972 – 1,053
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34.8	€ 2,818.80

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 2 April 2020.

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

Berlin, 2 April 2020

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

Prof. Hecken