Atezolizumab (Reassessment Based on New Scientific Knowledge: Urothelial Carcinoma)

Resolution of: 16 March 2018
Entry into force on: 16 March 2018
BAnz AT 17 04 2018 B2

Resolution of: 2 August 2018
Entry into force on: 2 August 2018
BAnz AT 28 08 2018 B2

Resolution of: 20 June 2019
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BAnz AT 30 07 2019 B2

Resolution of: 15 April 2021
Entry into force on: 15 April 2021
BAnz AT 06 05 2021 B6

Resolution of: 6 April 2023
Entry into force on: 6 April 2023
BAnz AT 17 05 2023 B5

Valid until: unlimited

New therapeutic indication (according to the marketing authorisation of 2 July 2018):

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC)

- after prior platinum-based chemotherapy or
- who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥ 5%.

Note:

The resolution of 20 June 2019 relates exclusively to the assessment of the additional benefit of atezolizumab in the sub-population: a) Urothelial carcinoma; patients who are not eligible for a treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5% (first line)

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

a) <u>Urothelial carcinoma; patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5% (first line)</u>

Appropriate comparator therapy:

Chemotherapy according to the doctor's instructions

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

An additional benefit is not proven.

Study results according to endpoints:

a) Urothelial carcinoma; patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5% (first line)

There are no data that would allow for the assessment of the additional benefit.

b) **Patients with prior platinum-containing therapy**

Appropriate comparator therapy:

a) For patients with an early relapse (≤ 6 months)

- Vinflunine

b) For patients with a late relapse (> 6 – 12 months)

- Vinflunine

or

- Renewed cisplatin-containing chemotherapy (for patients who, depending on the course of the disease, general condition, and tolerability of the first-line therapy, are eligible for it)

Extent and probability of the additional benefit compared with vinflunine:

Hint for a minor additional benefit.

Study results according to endpoints:

1. Patients who are ineligible for cisplatin-containing therapy (first-line)

There is no data that would allow for the assessment of the additional benefit.

2. Patients with prior platinum-containing therapy

Results of the IMvigor211 study[1]:

Endpoint category Endpoint		Atezolizumab		Vinflunine	Atezolizumab vs vinflunine
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR[b] [95% CI]; p value[c]
Mortality					

[1] Data from the IQWiG dossier evaluation (A17-52); results for endpoint PFS from the dossier of the pharmaceutical company.

Endpoint category Endpoint		Atezolizumab		Vinflunine	Atezolizumab vs vinflunine
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR[b] [95% CI]; p value[c]
Overall survival (13 March 2017)	252	9.2 [7.9; 10.4] 178 (70.6)	250	8.3 [6.9; 9.6] 184 (73.6)	0.97 [0.78; 1.19]; 0.752
Morbidity					
Progression-free survival (PFS)					
PFS (13 March 2017)	252	2.1 [2.1; 2.2] 220 (87.3)	250	4.1 [3.7; 4.3] 218 (87.2)	1.19 [0.98; 1.44]; 0.0782
EORTC QLQ-C30 – symptomatology (time until deterioration[d])					
Fatigue	238	1.4 [0.9; 1.5] 172 (72.3)	230	1.0 [0.8; 1.4] 166 (72.2)	0.80 [0.64; 1.00]; 0.049
Nausea and vomiting	238	5.5 [3.0; 7.6] 111 (46.6)	230	2.8 [2.1; 3.7] 111 (48.3)	0.74 [0.56; 0.97]; 0.031
Pain	238	2.1 [1.5; 2.5] 151 (63.4)	230	1.8 [1.4; 2.4] 132 (57.4)	0.98 [0.76; 1.25]; 0.848
Dyspnoea	237	3.5 [2.8; 5.8] 119 (50.2)	229	3.7 [2.3; 6.0] 102 (44.5)	0.96 [0.73; 1.27]; 0.774
Insomnia	238	3.7 [3.2; 6.4] 115 (48.3)	230	2.8 [2.0; 4.0] 117 (50.9)	0.74 [0.56; 0.96]; 0.026
Loss of appetite	237	2.1 [1.5; 4.2] 132 (55.7)	230	1.9 [1.4; 3.0] 121 (52.6)	0.99 [0.76; 1.28]; 0.924
Constipation	238	4.2 [3.0; 5.6] 113 (47.5)	228	1.9 [1.4; 3.7] 112 (49.1)	0.73 [0.55; 0.96]; 0.023
Diarrhoea	238	6.2 [4.2; 8.4] 98 (41.2)	228	4.9 [3.7; 14.8] 87 (38.2)	0.87 [0.65; 1.18]; 0.375
Health-related quality of life					
EORTC QLQ-C30 – global health status health status and functional scales (time until deterioration[d])					
Global health status	236	2.2 [1.5; 2.9] 148 (62.7)	229	1.8 [1.5; 2.3] 130 (56.8)	0.92 [0.71; 1.18]; 0.503
Physical function	238	2.1 [1.5; 2.3] 152 (63.9)	230	1.7 [1.4; 2.3] 132 (57.4)	0.95 [0.75; 1.22]; 0.699
Role function	238	1.8 [1.4; 2.2] 152 (63.9)	229	1.4 [1.3; 1.6] 146 (63.8)	0.85 [0.67; 1.08]; 0.180
Emotional function	238	4.6 [3.1; 7.7]	229	4.2 [2.9; 5.8]	0.90 [0.68; 1.20];

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		115 (48.3)		98 (42.8)	0.484
Cognitive function	238	2.8 [2.2; 3.5] 124 (52.1)	229	2.3 [1.7; 3.1] 118 (51.5)	0.88 [0.68; 1.15]; 0.352
Social function	238	2.2 [1.7; 2.8] 143 (60.1)	229	1.4 [1.4; 1.8] 135 (59.0)	0.81 [0.64; 1.04]; 0.100
Side effects					
AE (additionally shown)	247	no data available 235 (95.1)	242	no data available 238 (98.3)	–
Severe AE (CTCAE grade ≥ 3)	247	no data available 141 (57.1)	242	no data available 164 (67.8)	0.57 [0.45; 0.72]; < 0.001[e]
SAE	247	no data available 102 (41.3)	242	no data available 130 (53.7)	0.58 [0.45; 0.76]; < 0.001[e]
Discontinuation because of AE	247	22 (8.9)	242	38 (15.7)	RR: 0.57 [0.35; 0.93]; 0.024[f]
Specific AE					
Immune mediated AE[g]	No usable data available[h]				
Immune mediated SAE[g]	No data available for the relevant sub-population[h]				
Immune mediated severe AE[g] (CTCAE grade ≥ 3)	247	14 (5.7)[i]	242	1 (0.4)	RR: 13.72 [1.82; 103.50]; < 0.001[f]
Constipation (CTCAE grade ≥ 3)	247	no data available 2 (0.8)	242	no data available 21 (8.7)	0.09 [0.02; 0.38]; 0.001[e]
Neutropoenia (CTCAE grade ≥ 3)	247	0 (0)	242	38 (15.7)[i]	RR: 0.01 [0.00; 0.21]; < 0.001[f]
Febrile neutropoenia (CTCAE grade ≥ 3)	247	no data available 1 (0.4)	242	no data available 21 (8.7)[i]	0.04 [0.01; 0.32]; 0.002[e]
Respiratory, thoracic, and mediastinal disorders (SAE)	247	10 (4.0)	242	1 (0.4)	RR: 9.80 [1.26; 75.95]; 0.007[f]
Pneumonitis (SAE)	247	4 (1.6)	242	0 (0)	RR: –[j] 0.048[f]
Mucous membrane inflammation	247	no data available 12 (4.9)	242	no data available 35 (14.5)	0.28 [0.15; 0.55]; < 0.001[e]

a: Calculated according to Brookmeyer-Crowley method
b: Unless otherwise stated, calculated by Cox model, stratified by PD-L1 status, presence of liver metastases, and

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number of risk factors
c: Stratified log-rank test
d: Time until deterioration of the score by at least 10 points compared with baseline
e: Calculated by unstratified Cox model
f: Own calculation of RR, CI (asymptotic) and p value (unconditional exact test, CSZ method)
g: Defined as AE requiring the use of corticosteroids for control and lacking clear aetiology
h: Operationalisation of the total rates of immune-mediated AE is inappropriate. No data on immune-mediated SAE.
i: Own calculation
j: Effect estimator and 95% CI cannot be interpreted meaningfully

Abbreviations used: CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; HR: hazard ratio; CI: confidence interval; n: number of patients with (at least one) event; N: number of patients evaluated; PD-L1: programmed cell death ligand-1; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event, AE: adverse event; vs: versus

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

a) Urothelial carcinoma; patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5% (first line)

approx. 220 to 380 patients

b) Patients with prior platinum-containing therapy

approx. 1,500 to 1,900 patients

3. Requirements for a quality-assured application

The requirements of 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: 2 May 2019):

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

Only specialists in internal medicine, haematology, and oncology with experience treating patients with urothelial carcinoma, specialists in urology, and specialists participating in the Oncology Agreement may initiate and monitor treatment with atezolizumab.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material and a patient card. Patients are requested to carry their patient cards with them at all times. The training material for health professionals and the patient card shall include, in particular, instructions on how to deal with the potential immune-mediated adverse reactions to atezolizumab as well as infusion reactions

4. Treatment costs

a) Urothelial carcinoma; patients who are not eligible for treatment with cisplatin and whose tumours have a PD-L1 expression ≥ 5% (first line)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Atezolizumab	€ 75,234.01
Appropriate comparator therapy:	
patient-individualized	

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 June 2019)

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ Unit	Number/ cycle	Number/ Patient/ year	Costs/ Patient/ year
Atezolizumab	a)	€ 71	1	17	€ 1,207
a) Surcharge for the preparation of a parenteral solution containing monoclonal antibodies”					

Annual treatment costs:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Atezolizumab	€ 101,818.78
Appropriate comparator therapy	
1. Patients who are ineligible for cisplatin-containing therapy (first-line)	
different for each individual patient	
2. Patients with prior platinum-containing therapy	
Vinflunine	€ 66,446.20
Cisplatin monotherapy[2] (dosing scheme 1) *Additionally required SHI services* Total	€ 928.07 – 3,173.05 *€ 127.06 – 413.74* € 1,055.13 – 3,586.79
Cisplatin monotherapy[2] (dosing scheme 2) *Additionally required SHI services* Total	€ 2,851.55 – 3,728.95 *€ 635.31 – 1,294.34* € 3,486.86 – 5,023.29
Cisplatin + gemcitabine[2] *Additionally required SHI services* Total	€ 6,914.70 *(cisplatin: € 1,498.38, gemcitabine: € 5,416.32)* *€ 245.49 – 316.39* € 7,160.19 – 7,231.09

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 February 2018

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year	Cost per patient per year
Type of service: *a = Surcharge for the preparation of a parenteral solution containing monoclonal antibodies* *b = Surcharge for production of a parenteral preparation containing cytostatic agents*					
Medicinal product to be assessed					
Atezolizumab	a	€ 71	1	17	€ 1,207
Appropriate comparator therapy					
1. Patients who are ineligible for cisplatin-containing therapy (first-line)					

[2] In accordance with the appropriate comparator therapy, renewed cisplatin-containing chemotherapy can only be considered for patients with relapse after at least 6 – 12 months.

different for each individual patient					
2. Patients with prior platinum-containing therapy					
Vinflunine	b	€ 81	1	17	€ 1,377
Cisplatin monotherapy	b	€ 81	1 – 5	13 – 85	€ 1,053 – 6,885
Cisplatin + gemcitabine					
Cisplatin	b	€ 81	1	13	€ 1,053
Gemcitabine	b	€ 81	3	39	€ 3,159