Cemiplimab (new therapeutic indication: cervical cancer, pretreated)

Resolution of: 19 October 2023 valid until: unlimited
Entry into force on: 19 October 2023
Federal Gazette, BAnz AT 22 11 2023 B4

New therapeutic indication (according to the marketing authorisation of 18 November 2022):

LIBTAYO as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

Therapeutic indication of the resolution (resolution of 19 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) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy

Appropriate comparator therapy:

Therapy according to doctor's instructions under selection of a monotherapy with:

- Nab-paclitaxel
- Vinorelbine
- Ifosfamide
- Topotecan
- Pemetrexed
- Irinotecan
- Pembrolizumab (for patients with PD-L1 positive cervical cancer)

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

Indication of a considerable additional benefit.

b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy

Appropriate comparator therapy:

- Best supportive care

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

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	↑	Advantage in the symptom scales of pain, nausea and vomiting and loss of appetite
Health-related quality of life	↑	Advantage in physical functioning, role functioning and social functioning.
Side effects	↑↑	Advantage in the endpoint of severe adverse events (severe AEs). In detail, advantages in specific AEs.
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		

EMPOWER-Cervical 1 study: Cemiplimab **vs** therapy according to doctor's instructions under selection of a monotherapy with gemcitabine, irinotecan, pemetrexed, topotecan or vinorelbine (hereafter: chemotherapy).

Relevant sub-population: Patients for whom treatment with irinotecan, pemetrexed, topotecan or vinorelbine had been selected prior to randomisation, i.e. gemcitabine was excluded from the analysis.

Study design: open-label RCT

Data cut-off: 04.01.2021

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A23-36) unless otherwise indicated.

Mortality

Endpoint	Cemiplimab		Chemotherapy[a]		Cemiplimab vs chemotherapy[a]
	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)[b]
Overall survival					
	196	12.7 [8.9; 15.2] *119 (60.7)*	183	8.0 [7.0; 9.7] *131 (71.6)*	0.68 [0.53; 0.87] 0.003[c] AD = + 4.7 months

Morbidity

Endpoint	Cemiplimab		Chemotherapy[a]		Cemiplimab vs chemotherapy[a]
	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)[b]
Progression-free survival (PFS)[d]					
	196	2.8 [2.3; 3.9] *160 (81.6)*	183	2.9 [2.7; 3.7] *165 (90.2)*	0.77 [0.62; 0.97] 0.0245 AD = - 0.1 months
Symptomatology (EORTC QLQ-C30) Time to 1st deterioration[e]					
Fatigue	196	2.8 [1.7; 3.2] *111 (56.6)*	183	2.0 [1.7; 2.9] *97 (53.0)*	0.82 [0.62; 1.09] 0.160[f]
Pain	196	4.3 [2.9; 5.8] *85 (43.4)*	183	2.8 [1.8; 2.9] *91 (49.7)*	0.63 [0.47; 0.86] 0.003[f] AD = + 1.5 months
Nausea and vomiting	196	7.8 [6.3; 12.0] *70 (35.7)*	183	3.0 [1.8; 5.2] *82 (44.8)*	0.44 [0.31; 0.61] < 0.001[f] AD = + 4.8 months
Dyspnoea	196	7.6 [5.7; 19.3] *69 (35.2)*	183	5.9 [4.4; 9.9] *62 (33.9)*	0.75 [0.52; 1.07] 0.107[f]
Insomnia	196	4.4 [3.2; 8.0] *78 (39.8)*	183	4.3 [2.9; 7.0] *70 (38.3)*	0.81 [0.58; 1.12] 0.195[f]

Loss of appetite	196	5.7 [4.2; 8.4] *80 (40.8)*	183	3.1 [2.6; 4.4] *84 (45.9)*	0.58 [0.42; 0.80] < 0.001[f] AD = + 2.6 months
Constipation	196	8.2 [5.7; 10.1] *74 (37.8)*	183	4.4 [3.1; 7.0] *65 (35.5)*	0.72 [0.51; 1.01] 0.055[f]
Diarrhoea	196	8.4 [7.1; 18.0] *58 (29.6)*	183	8.8 [5.6; n.c.] *48 (26.2)*	0.82 [0.56; 1.22] 0.323[f]

Health-related quality of life

Endpoint	**Cemiplimab**		**chemotherapy[a]**		**Cemiplimab vs chemotherapy[a]**
	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)[b]
Symptomatology (EORTC QLQ-C30) Time to 1st Deterioration[g]					
Global health status	196	5.8 [4.4; 7.1] *87 (44.4)*	183	3.5 [2.8; 4.4] *84 (45.9)*	0.75 [0.55; 1.03] 0.071[f]
Physical functioning	196	6.2 [5.3; 10.5] *89 (45.4)*	183	4.1 [2.9; 4.8] *83 (45.4)*	0.62 [0.45; 0.85] 0.003[f] AD = + 2.1 months
Role functioning	196	4.3 [2.8; 8.3] *91 (46.4)*	183	2.8 [1.8; 3.5] *89 (48.6)*	0.62 [0.46; 0.85] 0.002[f] AD = + 1.5 months
Emotional functioning	196	7.3 [5.6; 13.8] *68 (34.7)*	183	5.3 [3.5; 7.1] *64 (35.0)*	0.72 [0.50; 1.02] 0.062[f]
Cognitive functioning	196	5.6 [3.1; 7.2] *90 (45.9)*	183	3.2 [2.9; 5.2] *72 (39.3)*	0.85 [0.62; 1.16] 0.285[f]
Social functioning	196	5.8 [4.4; 11.3] *76 (38.8)*	183	4.2 [2.9; 5.7] *78 (42.6)*	0.65 [0.47; 0.91] 0.009[f] AD = + 1.6 months

Side effects

Endpoint	Cemiplimab		Chemotherapy		Cemiplimab vs chemotherapy
	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)[b]
Total adverse events (presented additionally)[h]					
	195	0.6 [0.4; 0.7] *173 (88.7)*	172	0.2 [0.1; 0.3] 152 (88.4)	–
Serious adverse events (SAE)[h]					
	195	n.r. [13.6; n.c.] *56 (28.7)*	172	n.r. [7.8; n.c.] *52 (30.2)*	0.77 [0.53; 1.14] 0.189[i]
Severe adverse events (CTCAE grade ≥ 3)[h]					
	195	7.2 [4.8; 13.8] *94 (48.2)*	172	3.6 [1.9; 11.6] 87 (50.6)	0.69 [0.52; 0.94] 0.017[i] AD = + 3.6 months
Therapy discontinuation due to adverse events					
	195	n.r. *20 (10.3)*	172	n.r. *8 (4.7)*	1.59 [0.69; 3.68] 0.275[i]
Specific adverse events					
Immune-mediated SAEs					
	No data				
Immune-mediated severe AEs (CTCAE grade ≥ 3)					
	No suitable data				
Other specific AEs					
Nausea (PT, AEs)	195	n.r. *42 (21.5)*	172	7.8 [5.3; n.c.] *66 (38.4)*	0.43 [0.29; 0.64] < 0.001[i]
Blood and lymphatic system disorders (SOC, SAEs)	195	n.r. *2 (1.0)*	172	n.r. *17 (9.9)*	0.09 [0.02; 0.40] < 0.001[i]
Hepatobiliary disorders (SOC,	195	n.r. *10 (5.1)*	172	n.r. *1 (0.6)*	7.52 [0.96; 58.87]

severe AEs; CTCAE grade ≥ 3)					0.024[i]

a) Chemotherapy applied in the EMPOWER-Cervical 1 study was pemetrexed, topotecan, irinotecan, gemcitabine or vinorelbine as monotherapy. Patients for whom treatment with gemcitabine was selected prior to randomisation were not included in the analyses.
b) Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
c) HR and CI: Cox proportional hazards model; p value: log-rank test. Each stratified by histology status (squamous cell carcinoma versus adenocarcinoma / adenosquamous carcinoma) and geographic region (North America versus Asia versus rest of the world).
d) Data from the dossier of the pharmaceutical company (Module 4D) of 18 April 2023.
e) Time to first deterioration An increase in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
f) HR and CI: Cox proportional hazards model; p value: log-rank test. Each stratified according to histology status (squamous cell carcinoma versus adenocarcinoma / adenosquamous carcinoma). Discrepant information between methodology section and results tables on whether stratification by geographic region (North America versus Asia versus rest of the world) was also done.
g) Time to first deterioration A decrease in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
h) Progression events of the underlying disease were not collected as AEs.
i) HR and CI: unstratified Cox proportional hazards model; p value: unstratified log-rank test

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; 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; PT: preferred term; RCT: randomised controlled trial; SOC: system organ class; SAE: serious adverse event; AE: adverse event; vs: versus.

b) <u>Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy</u>

There are no assessable data.

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 are 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 recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy

and

b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy

approx. 380 - 1,450 patients in total

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 Libtayo (active ingredient: cemiplimab) at the following publicly accessible link (last access: 10 October 2023):

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

Therapy with cemiplimab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with cervical cancer.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card).

The training material contains, in particular, information and warnings about immune-mediated side effects as well as infusion-related reactions.

4. Treatment costs

Annual treatment costs:

The costs for the first year of treatment are shown for the cost representation in the resolution.

a) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Cemiplimab	€ 80,879.55
Appropriate comparator therapy:	
Ifosfamide	
Ifosfamide	€ 10,528.74 - € 14,604.69 (21-day cycle) or € 7,866.30 - € 10,911.55 (28-day cycle)
Additionally required SHI services: *Mesna*	€ 1,345.30 - € 2,017.95 (21-day cycle) or € 1,005.11 - € 1,507.66 (28-day cycle)
Irinotecan	€ 26,088.55
Nab-paclitaxel	€ 63,817.63
Pembrolizumab	€ 93,515.26
Pemetrexed	€ 17,088.19
Additionally required SHI services	€ 118.49 - € 156.20
Topotecan	€ 18,538.83
Vinorelbine	€ 5,686.60

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 October 2023)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed					
Cemiplimab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
Appropriate comparator therapy:					
Ifosfamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	5	65.0 or 87.0	€ 6,500 or € 8,700
Irinotecan	Surcharge for production of a parenteral preparation	€ 100	1	52.1	€ 5,210

	containing cytostatic agents				
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	52.2	€ 5,220
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Topotecan	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	5	87.0	€ 8,700
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	34.8	€ 3,480

b) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Cemiplimab	€ 80,879.55
Best supportive care	Different from patient to patient
Appropriate comparator therapy:	

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

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 October 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
Medicinal product to be assessed					
Cemiplimab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740

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) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are eligible for further antineoplastic 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) Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based first-line chemotherapy who are ineligible for further antineoplastic 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.