Gemeinsamer Bundesausschuss

Olaparib (New Therapeutic Indication: Ovarian carcinoma, fallopian tube carcinoma or primary peritoneal carcinoma; maintenance treatment after first-line therapy; HRD-positive; combination with bevacizumab)

Resolution of: 3 June 2021 Valid until: 1 October 2022
Entry into force on: 3 June 2021
BAnz AT 23 07 2021 B3

New therapeutic indication (according to the marketing authorisation of 3 November 2020):

Lynparza in combination with bevacizumab is indicated for the:

Maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapyin combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability.

Therapeutic indication of the resolution (resolution of 3/6/2021):

see therapeutic indication according to marketing authorisation.

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

Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma who have a response (complete or partial) after completion of a platinum treatment as part of first-line chemotherapy regimen in combination with bevacizumab; disease associated with homologous recombination deficiency (defined by either a BRCA1/2-mutation and/or genomic instability); maintenance treatment:

Appropriate comparator therapy:

– Continuation of treatment with bevacizumab started with platinum treatment as part of first-line chemotherapy regimen.

Extent and probability of additional benefit of olaparib in combination with bevacizumab compared with bevacizumab:

An additional benefit is not proven.

Study results according to endpoints:

Summary of results of relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↔	no relevant difference for the benefit assessment
Morbidity	↔	Advantages in the endpoints Insomnia, Hormonal symptoms, Side effects of chemotherapy; Disadvantages in the endpoints Nausea and vomiting, Loss of appetite; overall, no predominant advantage or disadvantage
Health-related quality of life	↔	no relevant difference for the benefit assessment
Side effects	↓	Disadvantage in the endpoint Discontinuation due to AE as well as in detail predominantly disadvantages with specific AE
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 a 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		

PAOLA-1 study: Olaparib + bevacizumab **vs** bevacizumab[1,2]

Study design: randomised, double-blind, two-armed

Relevant sub-population: Patients whose tumour is associated with a positive HRD status (BRCA 1/2-mutation and/or genomic instability) (approximately 48.0% of the study population)

[1] Data from the dossier assessment of the IQWiG (A20-111) and from the addendum (A21-55), unless otherwise indicated.
[2] Data cut-off 22.3.2020

Mortality

Endpoint	**Olaparib + Bevacizumab**		**Bevacizumab**		Intervention vs Control
	N	Median time to the event in months [95% CI] *Patients with event n (%)*	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	255	n.a. 61 (23.9)	132	n.a. 42 (31.8)	0,70 [0.47; 1.05] 0.078
Effect modification by the "outcome of first-line therapy" feature					
NED (PDS)[b]	92	n.a. 8 (8.7)	48	n.a. 14 (29.2)	0,26 [0.11; 0.61] 0,002
NED/CR (IDS)[c]	74	n.a. 23 (31.1)	38	n.a. 11 (28.9)	1,04 [0.52; 2.23] 0,904
NED/CR (chemo)[d]	40	n.a. 9 (22.5)	20	n.a. 8 (40.0)	0,54 [0.21; 1.45] 0,216
PR[e]	49	44,0 [32.3; n.c.] 21 (42.9)	26	n.a. 9 (34.6)	1,13 [0.53; 2.60] 0,758
	Interaction: 0.043				
NED (PDS)[b] + NED/CR (chemo)[d]					0.36[f] 0.19 (0.68)[f] 0.002[f]
NED/CR (IDS)[c] + PR[e]					1.08[f] 0,63 (1,85)[f] 0.778[f]
	Interaction: 0.010[g]				

Morbidity

Endpoint	Olaparib + Bevacizumab		Bevacizumab		Intervention vs Control
	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Progression-free survival 1 (PFS 1)[lh]					
	255	42,6 [36.4; n.a.] 115 (45.1)	132	17,6 [15.8; 20.3] 100 (75.8)	0,39 [0.30; 0.51] <0.0001 25 months
Disease symptoms - time to deterioration[i]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	255	5,6 [3.1; 6.0] 199 (78.0)	132	5,7 [5.5; 11.1] 98 (74.2)	1,10 [0.86; 1.41] 0,482
Nausea and Vomiting	255	5,8 [5.6; 8.7] 178 (69.8)	132	19,2 [12.7; 23.5] 70 (53.0)	1,81 [1.37; 2.42] < 0.001 13.4 months
Pain	255	5,8 [5.6; 8.3] 183 (71.8)	132	5,6 [3.0; 8.1] 95 (72.0)	0,92 [0.72; 1.19] 0,551
Dyspnoea	255	20,7 [16.0; 52.5] 125 (49.0)	132	18,7 [12.3; 24.9] 67 (50.8)	0,92 [0.68; 1.25] 0,580
Insomnia	255	11,3 [8.4; 14.0] 159 (62.4)	132	8,3 [5.6; 11.1] 91 (68.9)	0,73 [0.56; 0.95] 0,019 3.0 months
Loss of Appetite	255	13,6 [11.1; 22.1] 146 (57.3)	132	22,3 [16.6; 28.7] 65 (49.2)	1,42 [1.06; 1.92] 0,023 8.7 months
Constipation	255	19,9 [16.6; 23.4]	132	19,7 [14.0; 22.3]	1,03 [0.77; 1.39]

Endpoint	Olaparib + Bevacizumab		Bevacizumab		Intervention vs Control
	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
		133 (52.2)		69 (52.3)	0,831
Diarrhoea	255	24,0 [16.6; 25.9] 124 (48.6)	132	23,5 [19.9; 35.0] 58 (43.9)	1,15 [0.84; 1.58] 0,409
Symptom scales of the EORTC QLQ-OV28					
abdominal/ gastrointestinal symptoms	255	11,1 [8.3; 14.0] 169 (66.3)	132	8,3 [5.7; 11.3] 89 (67.4)	0,88 [0.68; 1.15] 0,351
peripheral neuropathy	255	25,3 [18.6; n.c.] 114 (44.7)	132	23 [12.7; n.c.] 58 (43.9)	0,93 [0.68; 1.29] 0,654
hormonal Symptoms	255	19,1 [14.3; 24.2] 135 (52.9)	132	11,3 [5.6; 19.1] 76 (57.6)	0,75 [0.56; 0.996] 0.046 7.8 months
Chemotherapy side effects	255	17,9 [12.0; 24.6] 135 (52.9)	132	11,1 [8.3; 16.6] 82 (62.1)	0,75 [0.57; 0.997] 0,045 6.8 months
individual questions[j]	255	21,9 [16.6; 25.7] 127 (49.8)	132	19,4 [16.4; n.c.] 64 (48.5)	1,01 [0.75; 1.38] 0.954
sexual function	no usable data available[k]				
health status					
EQ-5D VAS (time to deterioration)[l]					
15 points	255	25.3 [17.5; n.c.] 116 (45.5)	132	26.7 [19.9; n.c.] 58 (43.9)	1,05 [0.77; 1.46] 0.749
10 points.	255	11.1 [8.3; 13.9]	132	16,4 [9.6; 21.9]	1,15 [0.87; 1.52]

Endpoint	Olaparib + Bevacizumab		Bevacizumab		Intervention vs Control
	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
		156 (61.2)		78 (59.1)	0,346
7 points.	255	11,1 [8.3; 13.9] 156 (61.2)	132	16,4 [9.6; 21.9] 78 (59.1)	1,15 [0.88; 1.52] 0,333

Health-related quality of life

Endpoint	Olaparib + Bevacizumab		Bevacizumab		Intervention vs Control
	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Health-related quality of life - time to deterioration[m]					
Global health status and functional scales of the EORTC QLQ-C30					
global health status	255	16.6 [11.5; 21.8] 146 (57.3)	132	13.8 [9.3; 17.2] 81 (61.4)	0.85 [0.65; 1.12] 0.234
Physical function	255	20 [13.9; 52.5] 125 (49.0)	132	16.4 [11.5; 22.4] 74 (56.1)	0.85 [0.64; 1.14] 0,279
Role function	255	8,4 [5.8; 11.2] 167 (65.5)	132	9,3 [6.1; 16.2] 82 (62.1)	1,11 [0.85; 1.46] 0,450
Cognitive function	255	11,1 [8.5; 14.0] 174 (68.2)	132	8,5 [5.9; 13.6] 85 (64.4)	0,91 [0.70; 1.19] 0.484
Emotional function	255	13,8 [9.0; 19.3]	132	11,1 [8.3; 13.8]	0,93 [0.71; 1.22]

Endpoint	**Olaparib + Bevacizumab**		**Bevacizumab**		Intervention vs Control
	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
		158 (62.0)		85 (64.4)	0,571
Social function	255	13,5 [8.6; 19.6] 148 (58.0)	132	11,3 [8.5; 16.4] 81 (61.4)	0,91 [0.69; 1.20] 0,471
Scales of the EORTC QLQ-OV28[i]					
Body image	255	21,9 [12.7; n.c.] 126 (49.4)	132	18,7 [11.5; 25.1] 71 (53.8)	0,93 [0.70; 1.26] 0,638
Attitude towards disease/treatment	255	12.2 [8.3; 24.1] 134 (52.5)	132	17.5 [11.2; n.c.] 65 (49.2)	1.15 [0.86; 1.57] 0.362

(continuation)

Side effects

Endpoint	Olaparib + Bevacizumab		Bevacizumab		Intervention vs Control
	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Adverse events (AEs) presented additionally					
	255	0.2 [0.2; 0.3] 255 (100)	131	0.3 [0.2; 0.7] 127 (96.9)	-
Serious adverse events (SAE)					
	255	n.a. 73 (28.6)	131	n.a. 45 (34.4)	0.75 [0.52; 1.10] 0.133
Severe adverse events (CTCAE grade ≥ 3)					
	255	8.6 [5.6; 15.3] 147 (57.6)	131	16.7 [6.6; n.c.] 65 (49.6)	1.20 [0.90; 1.63] 0.221
Discontinuation due to AE					
	255	n.a. 50 (19.6)	131	n.a. 8 (6.1)	3.14 [1.57; 7.18] 0.002
Specific adverse events					
myelodysplastic syndrome and acute myeloid leukaemia (PT, UE)[n, o]	255	n.a. 2 (0.8)	131	n.a. 2 (1.5)	0.54 [0.06; 4.51] 0.531
Pneumonitis (PT, AE)[n]	255	n.a. 3 (1.2)	131	n.a. 0 (0)	n.a. 0.195
Nausea (PT, AE)[n]	255	2.9 [0.8; 16.0] 144 (56.5)	131	n.a. 33 (25.2)	3.10 [2.14; 4.63] < 0.001
Anaemia (PT severe AE)[n]	255	n.a. 47 (18.4)	131	n.a. 1 (0.8)	27.79 [6.08; 492.43]

Endpoint	Olaparib + Bevacizumab		Bevacizumab		Intervention vs Control
	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	N	Median time to to the event in Months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
					< 0.001
Fatigue and asthenia (PT, severe AE)[n]	255	n.a. 17 (6.7)	131	n.a. 2 (1.5)	4.54 [1.29; 28.70] 0.027
Hypertonia (PT, severe AE)[n]	255	n.a. 50 (19.6)	131	n.a. 42 (32.1)	0.52 [0.34; 0.79] 0.002

(continuation)

Endpoint	Olaparib + Bevacizumab		Bevacizumab		Intervention vs Control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value
Specific adverse events					
myelodysplastic syndrome	255	1 (0.4)	131	1 (0.8)	0.51 [0.03; 8.15] 0.637
acute myeloid leukaemia	255	2 (0.8)	131	1 (0.8)	1.03 [0.09; 11.23] 0.982

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] Patients without detectable tumour after primary surgery
[c] Patients without detectable tumour/with complete response after interval surgery
[d] Patients without detectable tumour/with complete response after chemotherapy
[e] patients with partial response
[f] IQWiG calculation; fixed-effect meta-analysis (inverse variance method)
[g] IQWiG's own calculation, Q-test
[h] Data from: Olaparib Module 4A dossier dated 30.11.2020
[i] Time to deterioration; defined as an increase in score of ≥ 10 points from baseline
[j] The individual questions included in this scale relate to the presence of

Endpoint	Olaparib + Bevacizumab		Bevacizumab		Intervention vs Control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value

Indigestion or heartburn, hair loss and altered sense of taste.
According to the current scoring manual, this scale is no longer evaluated, but the individual questions are included in the evaluation of the other scales

[k] The pharmaceutical company did not submit any evaluations for the sexuality scale, as according to the scoring manual used, there is no scoring algorithm.

[l] Time to deterioration, defined as a decrease in score by ≥ 15, 10, and 7 points, respectively, in the comparison to baseline

[m] Time to deterioration; defined as a decrease in score by ≥ 10 points compared to baseline

[n] Follow-up until death or end of study

[o] discrepant data within module 4 A of the dossier; data for the endpoint MDS/ AML intervention vs. control n (%); HR [95% CI]; p: 2 (0.8) vs. 1 (0.8); 1.07 [0.10; 23.20]; 0.955

Abbreviations used:
AD = absolute difference; AML = acute myeloid leukaemia; BRCA = breast cancer susceptibility gene; CTCAE = Common Terminology Criteria for Adverse Events; CR = complete response; chemo = chemotherapy; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life Questionnaire - 5 Dimensions; HR = hazard ratio; IDS = interval surgery; CI = confidence interval; MDS = myelodysplastic syndrome; N = number of patients evaluated; n = number of patients with (at least one) event; n. b. = not calculable; n. a. = not achieved; NED = no detectable tumour; QLQ-C30 = Quality of Life Questionnaire - Core 30; QLQ-OV28 = Quality of Life Questionnaire - Ovarian Cancer 28; PDS = primary surgery; PR = partial response; PT = preferred term; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation; SE = standard error; tBRCA = tumour-BRCA; VAS = visual analogue scale; vs = versus

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

Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma who have a response (complete or partial) after completion of a platinum treatment as part of first-line chemotherapy regimen in combination with bevacizumab; disease associated with homologous recombination deficiency (defined by either a BRCA1/2-mutation and/or genomic instability); maintenance treatment:

approx. 1 030 patient

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 Lynparza (active ingredient: olaparib) at the following publicly accessible link (last access: 2 March 2021):

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

Treatment with olaparib should 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 ovarian carcinoma.

Prior to initiating treatment with Lynparza and bevacizumab for first-line maintenance treatment of epithelial ovarian carcinoma (EOC), fallopian tube carcinoma (FTC), or primary peritoneal carcinoma (PPC), patients must have a confirmed or suspected harmful BRCA1/2-mutation and/or genomic instability as determined by a validated testing method.

4. Treatment costs

Annual treatment costs:

Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma who have a response (complete or partial) after completion of a platinum treatment as part of first-line chemotherapy regimen in combination with bevacizumab; disease associated with homologous recombination deficiency (defined by either a BRCA1/2-mutation and/or genomic instability); maintenance treatment:

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Olaparib	€ 69,059,30
Bevacizumab	€ 63,626,29
Total:	€ 132,685,59
Appropriate comparator therapy:	
Continuation of treatment with bevacizumab started with platinum treatment as part of first-line chemotherapy regimen.	
Bevacizumab	€ 63,626,29

Cost after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 May 2021).

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ Patient/ Year	Costs Patient/ Year
Bevacizumab	Preparation of parenteral solutions with monoclonal antibodies	€ 71	15.7	15.7	€ 1,114.70