Olaparib (Lynparza®) plus bevacizumab as first-line maintenance treatment in patients with ovarian cancer

General information

Drug description [1]	Indication [2]
Olaparib is a poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor.	Olaparib 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 chemotherapy in 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.

Current treatment [3]

- Olaparib, niraparib and rucaparib are all indicated as monotherapies for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.
- NICE recommends olaparib within its marketing authorisation as an option for treating adults with relapsed, platinum sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum based chemotherapy only if:
  - they have had 3 or more courses of platinum based chemotherapy and
  - the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company
- NICE recommends niraparib for use within the Cancer Drugs Fund as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults, only if:
  - they have a germline BRCA mutation and have had 2 courses of platinum-based chemotherapy or
  - they do not have a germline BRCA mutation and have had 2 or more courses of platinum-based chemotherapy and
  - the conditions in the managed access agreement for niraparib are followed.

Regulatory status

EMA [2]

Approval status for this indication: On 17 September 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Lynparza®.

The CHMP adopted an extension of an existing indication for Lynparza® tablets as follows:

- Olaparib 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 chemotherapy in combination with bevacizumab and whose cancer is associated with HRD positive status defined by either a BRCA1/2 mutation and/or genomic instability.

Other indications:

- <u>Ovarian cancer</u>
  Olaparib is indicated as monotherapy for the:
  - maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
  - maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.
- <u>Breast cancer</u>
  - Olaparib is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should

FDA

Approval status for this indication: On 8 May 2020, the FDA expanded the indication of Lynparza® to include its combination with bevacizumab for first-line maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability [4].

Other indications: Olaparib is indicated:

- <u>Ovarian cancer:</u>
  - for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.
  - for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
  - for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.
- <u>Breast cancer</u>:
  - for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or

have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

- Adenocarcinoma of the pancreas
  - Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.
- Prostate cancer
  - Olaparib is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.

metastatic setting. Patients with hormone receptor-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.

- Pancreatic cancer:
  - for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.
- Prostate cancer:
  - for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone [5].

Costs

112 Lnyparza® tablets 150 mg = € 5,059.29 [6]

PAOLA-1 trial patients received olaparib tablets at a dose of 300 mg twice daily; according to this dosing regimen 28 days of olaparib treatment would cost € 5,059.29.

Special warnings and precautions for use [7]

- **Haematological toxicity:**
  - Haematological toxicity has been reported in patients treated with olaparib, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Patients should not start treatment with olaparib until they have recovered from haematological toxicity caused by previous anticancer therapy (haemoglobin, platelet and neutrophil levels should be ≤CTCAE grade 1). Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment. If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with olaparib should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of olaparib dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.
- **Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)**
  - The overall incidence of MDS/AML in patients treated in clinical trials with olaparib monotherapy, including long-term survival follow-up, was < 6 months to > 2 years. All patients had potential contributing factors for the development of MDS/AML; having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in germline breast cancer susceptibility gene 1 or 2 (gBRCA1/2) mutation carriers. The incidence of MDS/AML cases was similar among gBRCA1m and gBRCA2m patients (1.6% and 1.0%, respectively). Some of the patients had a history of previous cancer or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with olaparib, it is recommended that olaparib should be discontinued and the patient be treated appropriately.
- **Pneumonitis**
  - Pneumonitis, including events with a fatal outcome, has been reported in < 1.0% of patients treated with olaparib in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately.
- **Embryofoetal toxicity**
  - Based on its mechanism of action (PARP inhibition), olaparib could cause foetal harm when administered to a pregnant woman. Nonclinical studies in rats have shown that olaparib causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 300 mg twice daily.
- **Pregnancy/contraception**
  - Olaparib should not be used during pregnancy. Women of childbearing potential must use two forms of reliable contraception before starting olaparib treatment, during therapy and for 1 month after receiving the last dose of olaparib. Two highly effective and complementary forms of contraception are recommended. Male patients and their female partners of childbearing potential should use reliable contraception during therapy and for 3 months after receiving the last dose of olaparib.
- **Interactions**

- Olaparib co-administration with strong or moderate CYP3A inhibitors is not recommended. If a strong or moderate CYP3A inhibitor must be co-administered, the dose of olaparib should be reduced. Olaparib co-administration with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving olaparib requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of olaparib may be substantially reduced.

❖ **Sodium**

- This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg or 150 mg tablet, that is to say essentially "sodium-free".

Study characteristics [1, 8, 9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
PAOLA-1 NCT02477644	806	Olaparib tablets 300 mg twice daily	placebo	time from randomization until investigator-assessed disease progression or death	randomized, double-blind, international phase 3 trial	-	ARCAGY Research and others	Link

Efficacy (I vs. C)

Median investigator-assessed PFS: 22.1 months vs. 16.6 months; (HR for disease progression or death 0.59; 95% CI, 0.49-0.72; p<0.001)
Median PFS (assessed by blinded independent review): 26.1 vs. 18.3 months; (0.63; 95% CI, 0.51-0.77)
Median PFS (BRCA mutation): 37.2 vs. 21.7 months (0.31; 95% CI, 0.20-0.47)
Median PFS (BRCA negative): 18.9 vs. 16.0 months in the placebo group (0.71; 95% CI, 0.58-0.88)
Median PFS (HRD positive): 37.2 vs. 17.7 months (0.33; 95% CI, 0.25-0.45)
Median PFS (HRD positive/BRCA negative): 28.1 vs. 16.6 months (0.43; 95% CI, 0.28-0.66).
Median PFS (HRD negative/HRD unknown): 16.9 months vs.16.0 months in the placebo group (0.92; 95% CI, 0.72-1.17)
Median PFS (HRD negative): 16.6 vs. 16.2 months (1.00; 95% CI, 0.75-1.35)
Median time until the first subsequent treatment for all patients: 24.8 vs. 18.5 months (0.59; 95% CI, 0.49-0.71).
OS: data are immature
QoL: The adjusted mean change from baseline was −1.33 points (95% CI, −2.47 to −0.19) vs. −2.89 points (95% CI, −4.52 to −1.26). The estimated between-group difference was 1.56 points (95% CI, −0.42 to 3.55). None of these changes were considered to be clinically significant.

Safety (I vs. C)

Grade ≥3 AEs: n=303/535 (57%) vs. n=136/267 (51%)
SAEs: n=167/535 (31%) vs. n=83/267 (31%)
Death[1]: n=1/535 (<1%) vs. n=4/267 (1%)
Discontinuation[2]: n=109/535 (20%) vs. n=15/267 (6%)

ESMO-MCBS version 1.1 (overall population assessed by blinded independent review)

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	>6 m	PFS: +7.8 m	0.63 (0.51-0.77)	HR ≤0.65 AND Gain ≥3 m	3	-	ND	+1[3]	4
Adapted	NC	2b	>6 m	PFS: +7.8 m	0.63 (0.51-0.77)	HR ≤0.65 AND Gain ≥3 m	3	+6% grade ≥3 AEs, +14% discontinuation	ND	-1[4]	2

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	unclear[5]	yes[6]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia , BRCA=breast cancer gene, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CTCAE=Common Terminology Criteria for Adverse Events, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FIGO=The International Federation of Gynecology and Obstetrics, FM=final magnitude of clinical benefit grade, gBRCAm=germline BRCA-mutated, HER2= human epidermal growth factor receptor, HR=hazard ratio, HRD= homologous recombination deficiency, HRR= homologous recombination repair, I=intervention, Int.=intention, n=number, ND=no difference, m= months, mCRPC=metastatic castration-resistant prostate cancer, MDS=myelodysplastic syndrome, MG=median gain, n=number of patients, NICE=National Institute for

[1] death due to AE(s)
[2] discontinuation due to AE(s)
[3] Upgrade due to ≥10% improvement in PFS at 1 year
[4] downgrade due to >10% difference in the discontinuation rate
[5] Primary analysis data reported; the PAOLA-1 trial is ongoing until 06/2022
[6] The authors wrote the manuscript, with medical writing assistance funded by ARCAGY Research, AstraZeneca, and Merck Sharp & Dohme.

Health and Care Excellence, OS=overall survival, PARP= poly(adenosine diphosphate–ribose) polymerase, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

References:

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