Olaparib (Lynparza®) for metastatic castration-resistant prostate cancer (mCRPC)

General information

Drug description [1]	Indication [2]
Olaparib is a poly(adenosine diphosphate–ribose) polymerase (PARP)-inhibitor	Olaparib is indicated as monotherapy for the treatment of adult patients with mCRPC and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.

Current treatment [3]

- For men with mCRPC, NICE recommends:
  - Anti-androgen monotherapy with bicalutamide (to retain sexual function).
  - Docetaxel for men with hormone-refractory prostate cancer only if their Karnofsky performance-status score is 60% or more.
  - A corticosteroid such as dexamethasone (0.5 mg daily) as third-line hormonal therapy after androgen deprivation therapy and anti-androgen therapy to men with hormone-relapsed prostate cancer.
  - Bisphosphonates for pain relief may be considered for men with hormone-relapsed prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed.

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 a **new indication** for Lynparza® tablets as follows:

- Olaparib is indicated as monotherapy for the treatment of adult patients with mCRPC and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.

Other indications:

- **Ovarian cancer:**
  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.

  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.
- **Breast cancer**
  - 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 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**

FDA

Approval status for this indication: On 19 May 2020, the FDA approved Lynparza® for 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 [4].

Other indications: Olaparib is indicated:

- **Ovarian cancer**:
  - 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
  - in combination with bevacizumab for the 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
  - 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.
- **Breast cancer:**
  - 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 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:**

• 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.	• 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 [5].

Costs

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

PROfound 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. Median duration of treatment was 7.4 months.

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

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)

PROfound NCT02987543	387	Olaparib tablets (300 mg twice daily)	Pre-specified physician's choice of enzalutamide (160 mg once daily) or abiraterone (1,000 mg once daily, plus prednisone at a dose of 5 mg twice daily)	Imaging-based PFS in cohort A[1] according to BICR	Prospective, randomized, open-label, phase 3 trial	-	AstraZeneca and Merck Sharp & Dohme	Link

Efficacy (I vs. C)	**Safety** (I vs. C)
Cohort A: **Median imaging-based PFS:** 7.4 months vs. 3.6 months (HR for progression or death 0.34; 95% CI, 0.25-0.47; p<0.001) **Median radiological PFS in patients with BRCA1/2-mutated mCRPC by BICR (data cut off 4 June 2019):** 9.8 months vs. 3.0 months, HR 0.22, 95%CI 0.15-0.32) **Confirmed ORR:** 33% vs. 2% (odds ratio for an objective response, 20.86; 95% CI, 4.18-379.18; p<0.001) **Median time to pain progression:** HR 0.44; 95% CI, 0.22-0.91; p = 0.02 An interim analysis for OS was also conducted when 93 of 245 patients had died (data maturity, 38%): **median OS** of 18.5 months vs. 15.1 months (HR for death, 0.64; 95% CI, 0.43-0.97; p = 0.02). Among patients in the control group with independent review–confirmed imaging-based disease progression, **81% crossed over** to receive olaparib treatment at the investigators' discretion. **Median OS** in patients with BRCA1/2-mutated mCRPC **at data cut off 20 March 2020:** 20.1 months vs. 14.4 months, HR 0.63, 95% CI 0.42-0.95 **Overall population:** **Median imaging-based PFS (by independent review):** 5.8 vs. 3.5 months (HR 0.49; 95% CI, 0.38-0.63; p<0.001) **Confirmed ORR:** 22% vs. 4% (odds ratio, 5.93; 95% CI, 2.01-25.40). **Free from pain progression after 6 months:** 85% vs. 75% **Median OS at interim analysis (data maturity, 41%):** 17.5 vs. 14.3 months (HR for death, 0.67; 95% CI, 0.49-0.93) Among patients in the control group with independent review–confirmed imaging-based progression, **82% crossed over** to olaparib treatment. **PSA_{50} response:** confirmed in 30% vs. 10%	**Overall population (Cohorts A and B):** **Grade ≥3 AEs**: n=130/256 (51%) vs. n=49/130 (38%) **SAEs:** NR **Death[2]:** n=10/256 (4%) vs. n=5/130 (4%) **Discontinuation[3]:** n=46/256 (18%) vs. n=11/130 (8%)

ESMO-MCBS version 1.1 (cohort A)

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	>12 m ≤24 m	OS: + 3.2 m	OS: 0.63 (0.42-0.95)	HR ≤0.70 AND Gain ≥3-<5 m	3	-	-	-	3
Adapted	NC	2a	>12 m ≤24 m	OS: + 3.2 m	OS: 0.63 (0.42-0.95)	HR ≤0.70 AND Gain ≥3-<5 m	3	+13% grade 3 AEs, +10% discontinuation (based on the overall population)	-	-1	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	no	no, open-label	unclear[4]	yes[5]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia, BICR=blinded independent central review, 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=International Federation of Gynecology and Obstetrics, FM=final magnitude of clinical benefit grade, gBRCAm=germline BRCA-mutated, HER2=human epidermal growth factor receptor 2, HR=hazard ratio, HRD=homologous recombination deficiency, HRR= homologous recombination repair, I=intervention, Int.=intention, m=months, mCRPC=metastatic breast cancer gene, MDS=myelodysplastic syndrome, MG=median gain, n=number of patients, NICE=National

[1] Cohort A = Patients with at least one alteration in BRCA1, BRCA2, or ATM
[2] death due to AE(s)
[3] discontinuation due to AE(s)
[4] Interim analysis data; PROfound trial is ongoing until 12/2020
[5] The trial was designed by representatives of the sponsor in collaboration with the trial steering committee. The sponsor was responsible for overseeing the collection, analysis, and interpretation of the data. The sponsor provided input regarding the interpretation of the data. The manuscript was written with medical writing assistance funded by the sponsors, with critical review and input by the authors.

Institute for Health and Care Excellence, NR=not reported, SAE=serious adverse event, ORR=objective response rate, 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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7. European Medicines Agency (EMA). Lynparza: EPAR - Product information [Available from: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf.
8. Supplement to: de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382:2091-102. .