Olaparib (Lynparza®) in combination with abiraterone and prednisone or prednisolone for the treatment of metastatic castration-resistant prostate cancer (mCRPC)

General information

Drug description [1]	Indication [2]
Olaparib (Lynparza®) is a poly (adenosine diphosphate (ADP)-ribose) polymerase inhibitor; abiraterone is a next-generation hormonal agent.	Olaparib (Lynparza®) in combination with abiraterone and prednisone or prednisolone is indicated for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

Current treatment [3]

- **For men with mCRPC, before chemotherapy is indicated, NICE recommends:**
  - Abiraterone
    - Abiraterone in combination with prednisone or prednisolone is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:
      in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated.
      only when the company provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.
  - Enzalutamide
    - Enzalutamide is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:
      in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated.
      when the company provides it with the discount agreed in the patient access scheme.
- **If the above treatments are not preferred:**
  - Docetaxel
    - Docetaxel is recommended, within its licensed indications, as a treatment option for people with hormone-refractory prostate cancer only if their Karnofsky performance-status score is 60% or more.
  - It is recommended that treatment with docetaxel should be stopped:
    - at the completion of planned treatment of up to 10 cycles or
    - if severe adverse events occur or
    - in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies.
- Repeat cycles of treatment with docetaxel are **not recommended** if the disease recurs after completion of the planned course of chemotherapy.

Regulatory status

EMA [2]

Approval status for this indication: On 10 November 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Lynparza®.

<u>The CHMP adopted a new indication as follows:</u>

- Lynparza® is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

Other indications:

- Ovarian cancer
  - Lynparza® 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

FDA

Approval status for this indication: According to press release from the manufacturer, on 16 August 2022, the FDA granted priority review for the supplemental new drug application for olaparib (Lynparza®) in combination with abiraterone and prednisone or prednisolone for treatment of adult patients with mCRPC [4].

Other indications [5]: Lynparza® 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. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.
  - 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.

    Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.

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.
- 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 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
- Lynparza® is indicated as:
    - monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.
    - 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
- Lynparza® 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 recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

❖ Breast cancer
- for the adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCAm human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.
- 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. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.

❖ 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. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.

❖ Prostate cancer
- for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.

❖ Prostate cancer • Lynparza® is indicated: o 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.	

Costs

112 Lynparza® tablets 100 mg BP 2x56 = €4,325.56 (ex-factory price) [6].

Special warnings and precautions for use [7]

❖ **Haematological toxicity**
- Haematological toxicity has been reported in patients treated with Lynparza®, 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 Lynparza® 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 Lynparza® should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of Lynparza 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 Lynparza® monotherapy, including long-term survival follow-up, was <1.5%, with higher incidence in patients with BRCAm platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years. The majority of events had a fatal outcome. The duration of therapy with olaparib in patients who developed MDS/AML varied from <6 months to >4 years.
- If MDS/AML is suspected, the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged haematological toxicity, MDS/AML is confirmed, Lynparza® should be discontinued and the patient treated appropriately.

❖ **Venous Thromboembolic Events (VTE)**
- Venous thromboembolic events, predominantly events of pulmonary embolism, have occurred in patients treated with Lynparza® and had no consistent clinical pattern. A higher incidence was observed in patients with mCRPC, who also received ADT, compared with other approved indications.
- Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.
- Patients with a prior history of VTE may be more at risk of a further occurrence and should be monitored appropriately.

❖ **Pneumonitis**
- Pneumonitis, including events with a fatal outcome, has been reported in <1.0% of patients treated with Lynparza® 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, Lynparza® treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, Lynparza® treatment should be discontinued and the patient treated appropriately.

❖ **Embryofoetal toxicity**
- Based on its mechanism of action (PARP inhibition), Lynparza® 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**
- Lynparza® should not be used during pregnancy. Women of childbearing potential must use two forms of reliable contraception before starting Lynparza® treatment, during therapy and for 6 months after receiving the last dose of Lynparza®. 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 Lynparza®.

❖ **Interactions**
- Lynparza® 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 Lynparza® should be reduced. Lynparza co-administration with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving Lynparza® requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of Lynparza® 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)
PROpel NCT03732820	796 1:1	abiraterone (1000 mg once daily) plus prednisone or prednisolone with olaparib (300 mg twice daily)	abiraterone (1000 mg once daily) plus prednisone or prednisolone with placebo	Investigator-assessed imaging-based progression-free survival (ibPFS) or death from any cause in the absence of disease progression	double-blind, randomised, placebo-controlled phase 3 trial	-	AstraZeneca and Merck Sharp & Dohme , LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA	PROpel trial [1]

Efficacy (I vs. C), primary analysis data

Data cutoff 30 July, 2021

Median ibPFS: 24.8 vs. 16.6 months; HR 0.66; 95% CI, 0.54-0.81; p<0.001

Median ibPFS (prespecified sensitivity analysis by BICR): 27.6 vs. 16.4 months; HR 0.61; 95% CI, 0.49-0.74

Exploratory subgroup analysis of the PE

- ❖ An ibPFS benefit was observed across all prespecified subgroups whether evaluated by investigator assessment or by BICR.
- ❖ A global interaction test comparing the fit of a model with no interaction terms with a model with all subgroup interactions included was not significant at the 10% level (p=0.41), indicating a consistent treatment effect between subgroups.
- ❖ HRRm status was established for 535 patients (67.2%) by tumour tissue test, 734 (92.2%) by ctDNA test, and 778 (97.7%) by aggregated tumour tissue and ctDNA test results. The aggregate HRRm population included 226 patients (90 positive by tumour tissue and ctDNA, 28 positive by tumour tissue, and 108 positive by ctDNA), and the non-HRRm population included 552 patients (328 negative by tumour tissue and ctDNA, 38 negative by tumour tissue, and 186 negative by ctDNA).
- ❖ All HRs for the HRRm and non-HRRm populations favored I vs. C.
- ❖ Median ibPFS in both the HRRm and non-HRRm populations also suggested an improvement of ibPFS in these populations.

Secondary endpoints

OS data: immature at primary analysis data cutoff (28.6% maturity; HR 0.86; 95% CI, 0.66-1.12; p=0.29)

TFST: HR 0.74; 95% CI, 0.61-0.90

PFS2: HR 0.69; 95% CI, 0.51-0.94

Patients who received **subsequent therapies, n**: 132 vs. 173

HRQoL: Least-square mean change from baseline in FACT-P total score across all visits was -4.85 in the abiraterone and olaparib arm vs. -4.03 in the abiraterone and placebo arm (difference,-0.82 ; 95% CI, -3.56-1.92).

Safety (I vs. C), primary analysis data

Any AEs grade ≥3, n (%): 188/398 (47.2%) vs. 152/396 (38.4%)

Any serious AEs all grades, n (%): 135/398 (33.9%) vs. 107/396 (27.0%)

Any serious AEs grade ≥3: NA vs. NA

Discontinuation due to AEs:

Olaparib or placebo, n (%): 55/398 (13.8%) vs. 31/396 (7.8%)

Abiraterone, n (%): 34/398 (8.5%) vs. 35/396 (8.8%)

Death due to AE, n (%): 16/398 (4.0%) vs. 17/396 (4.3%)

Exploratory endpoints
ORR of 40.3% of patients with measurable disease at baseline: 58.4% vs. 48.1%; odds ratio 1.60; 95% CI, 1.02-2.53
Confirmed PSA response: 79.3% vs. 69.2%
Median time to PSA progression: not reached vs. 12.0 months, HR 0.55; 95% CI, 0.45-0.68

UPDATE: Interim OS (40% maturity) (data cut-off 14 March 2022) [7]
Number of events/total number of patients: 148/399 (37.1%) vs. 171/397 (43.1%)
Median time: NC vs. NC
HR 0.83 (95% CI, 0.66-1.03), p=0.1126
Patients alive at 36 months: 57.1% (95% CI, 50.6-63.0) vs. 51.6% (95% CI, 45.5-57.3)

Final OS (data cut-off 12 October 2022) [10]:
Maturity 47.9%, HR 0.81, 95% CI 0.67–1.00, p=0.0544
Median OS: 42.1 months vs. 34.7 months
Median OS in subgroups (18 patients with unknown HRRm status were excluded from subgroup analysis):

- HRRm (n = 226): NR vs. 28.5, HR 0.66 (95% CI, 0.45–0.95)
- Non-HRRm (n = 552): 42.1 vs. 38.9, HR 0.89 (95% CI, 0.70–1.14)
- BRCAm (n = 85): NR vs. 23.0, HR 0.29 (95% CI, 0.14–0.56)
- Non-BRCAm (n = 693): 39.6 vs. 38.0, HR 0.91 (0.73–1.13)

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	>6 months	ibPFS: + 8.2 months	0.66 (0.54-0.81)	HR ≤0.65 AND gain ≥1.5 months	3	-	-	-	3
Adapted	NC	2b	>6 months	ibPFS: + 8.2 months	0.66 (0.54-0.81)	HR>0.65	1	-	-	-	1

Risk of bias (RCT) [12]

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[1]	yes[2]	unclear

First published: 01/2023
Last updated: 04/2023

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, ctDNA=circulating tumour DNA, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACT-P=Functional Assessment of Cancer Therapy-Prostate Cancer, FDA=Food and Drug Administration, FIGO=International Federation of Gynaecology and Obstetrics, FM=final magnitude of clinical benefit grade, HR=hazard ratio, HRD=homologous recombination deficiency, HRRm=homologous recombination repair gene mutation, HRQoL=health-related quality of life, I=intervention, ibPFS=imaging-based progression-free survival, Int.=intention, mCRPC=metastatic castration-resistant prostate cancer, MDS=myelodysplastic syndrome MG=median gain, n=number of patients, NA=not applicable, NC=noncalculable, NHS=National Health Service, NICE=National Institute for Health and Care Excellence,

[1] Currently, primary analysis data is available. OS data were immature at the time of primary analysis cutoff date. Final (OS) data available as abstract only.
[2] Industry-funded.

ORR=objective response rate, OS=overall survival, PARP=poly(adenosine diphosphate-ribose) polymerase, PE=primary endpoint, PFS=progression-free survival, PFS2=time to second progression or death, PM=preliminary grade, PSA=prostate-specific antigen, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TFST=time to first subsequent therapy or death

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