Olaparib (Lynparza®) as monotherapy or in combination with endocrine therapy for the adjuvant treatment of patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer

General information

Drug description [1]	Indication [2]
Olaparib (Lynparza®) is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), and has been shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo either as a standalone treatment or in combination with established chemotherapies.	Olaparib (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.

Current treatment [3]

- For patients with early stage breast cancer the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines recommends:
  - Chemotherapy
    - It is recommended in the vast majority of triple-negative, HER2-positive breast cancers and in high-risk luminal-like HER2-negative tumours.
    - The most frequently used regimens contain anthracyclines and/or taxanes, although in selected patients cyclophosphamide/methotrexate/5 fluorouracil may still be used.
    - 4 cycles of doxorubicin and cyclophosphamide are considered to have equal efficacy to 6 cycles of cyclophosphamide/methotrexate/5 fluorouracil.

Regulatory status

EMA [2]

Approval status for this indication: On 23 June 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Lynparza®.

The CHMP adopted a new indication:

- 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.

Other indications: Lynparza® is indicated:

- Ovarian cancer
  - 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.
  - as monotherapy for the 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.
  - in combination with bevacizumab 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

FDA [4, 5]

Approval status for this indication: On 11 March 2022, the FDA approved olaparib (Lynparza®) for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Patients must be selected for therapy based on an FDA-approved companion diagnostic for olaparib.

- ✓ Priority review

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

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
  - 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
  - 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
  - as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer 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. 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 metastatic castration-resistant prostate cancer who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.

Costs

112 Lynparza® tablets 150 mg = € 4,677.09 (ex-factory price) [6].

Warnings and precautions [4]

- ❖ Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML)
  - Occurred in approximately 1.5% of patients exposed to Lynparza® monotherapy and the majority of events had a fatal outcome.
  - Monitor patients for haematological toxicity at baseline and monthly thereafter.
  - Discontinue if MDS/AML is confirmed.
- ❖ Pneumonitis
  - Occurred in 0.8% of patients exposed to Lynparza®, and some cases were fatal.
  - Interrupt treatment if pneumonitis is suspected.
  - Discontinue if pneumonitis is confirmed.
- ❖ Embryo-foetal toxicity
  - Can cause foetal harm.
  - Advise of the potential risk to a foetus and to use effective contraception.
- ❖ Venous thromboembolic events including pulmonary embolism occurred in 7% of patients with metastatic castration-resistant prostate cancer.
  - Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Study characteristics [7-10]

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

OlympiA NCT02032823	1,836 (1:1)	olaparib 300 mg tablets taken orally twice daily for 52 weeks	matching placebo tablets taken orally twice daily for 52 weeks	invasive disease–free survival	ongoing[1], prospective, multicenter, multinational, double-blind, phase 3 trial	HER2 BRCA1/BRCA2	National Cancer Institute and AstraZeneca	[9]

Efficacy (I vs. C)	Safety (I vs. C) (n=1,815)
Interim analysis data (data cutoff: 27 March 2020, median follow-up of 2.5 years) **Invasive disease-free survival at 3 years**: 85.9% vs. 77.1% (difference, 8.8 percentage points; 95% CI, 4.5-13.0); HR 0.58; 99.5% CI, 0.41-0.82; p<0.001 **Distant disease–free survival at 3 years**: 87.5% vs. 80.4% (difference, 7.1 percentage points; 95% CI, 3.0-11.1); HR 0.57; 99.5% CI, 0.39-0.83; p<0.001 Fewer **deaths** were reported in the olaparib group (n=59) than in the placebo group (n=86), with a HR of 0.68; 99% CI, 0.44-1.05; p= 0.02 (the between-group difference did not cross the prespecified multiple-testing procedure boundary for significance of p<0.01) UPDATE: Efficacy results **for** OS (10% maturity) – data cutoff 12 July 2021 [1] Number of events/total number of patients (%): 8% vs. 12%; HR 0.68 (98.5% CI, 0.47-0.97); p-value (2-sided)=0.0091 Percentage of patients alive at 3 years: 93% (95%CI, 91-94) vs. 89% (95% CI, 87-91) Percentage of patients alive at 4 years: 90% (95%CI,87-92) vs. 86% (95%CI, 84-89) QoL: ❖ The results of the European Organization for Research and Treatment of Cancer QLQ-C30 Global Health Status and Quality of Life scale indicated that global health quality did not decline during the 12 months of treatment with either olaparib or placebo. ❖ Any differences between the trial groups were **not** considered to be **clinically significant.**	**Serious AEs:** n=79/911 (8.7%) vs. n=76/904 (8.4%) **AEs leading to death:** n=1 (cardiac arrest) vs. n=2 (AML and ovarian cancer) **AEs that led to permanent discontinuation of the trial regimen:** n=90/911 (9.9%) vs. n=38/904 (4.2%)

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	Adjuvant	1	-	Invasive disease-free survival: +8.8 percentage points	0.58 (0.41-0.82)	Improvements in disease-free survival alone (HR<0.65) in studies without mature survival data	A	-	-	-	A
Adapted	Adjuvant	1	-	Invasive disease-free survival: +8.8 percentage points	0.58 (0.41-0.82)	Improvements in disease-free survival alone (HR<0.65) in studies without mature survival data	A	-	-	-	A

Risk of bias (RCT) [12]

[1] The OlympiA trial is currently ongoing; estimated study completion date is 05/2029.

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[2]	yes[3]	unclear
First published: 07/2022 Last updated: 11/2022					

Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukemia, BRCA=breast cancer gene, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, 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 Gynaecology 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, I=intervention, Int.=intention, MG=median gain, MDS=myelodysplastic syndrome, n=number of patients, OS=overall survival, PARP=poly(ADP-ribose) polymerase, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QLQ-C30=Cancer Quality of Life Questionnaire, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

References:

1. 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].
2. European Medicines Agency (EMA). Medicines. Lynparza. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/lynparza-1].
3. National Institute for Health Research (NIHR). Olaparib for BRCA mutated and high risk HER2 negative breast cancer - adjuvant therapy. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/14892-Olaparib-for-Breast-Cancer-v1.0-OCT2020-NON-CONF-.pdf].
4. U.S. Food and Drug Administration (FDA). Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208558s023lbl.pdf].
5. U.S. Food and Drug Administration (FDA). FDA approves olaparib for adjuvant treatment of high-risk early breast cance. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-adjuvant-treatment-high-risk-early-breast-cancer].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. Protocol for: Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. N Engl J Med 2021;384:2394-405.
8. Supplement to: Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. N Engl J Med 2021;384:2394-405.
9. Tutt AN, Garber JE, et al., for the OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med 2021;384:2394-405. [Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2105215].
10. U.S. National Library of Medicine, ClinicalTrials.gov. Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer (OlympiA). [Available from: https://clinicaltrials.gov/ct2/show/NCT02032823].
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
12. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].

[2] The OlympiA trial is ongoing; currently, only data from the prespecified interim analysis (reviewed by the independent data monitoring committee) is available.
[3] Industry-funded.