# 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-

### 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**

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**
  - 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.
  - 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 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)

**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)

**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.**

**Safety** (I vs. C) (n=1,815)

**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]**

| Adequate generation of randomisation sequence | Adequate allocation concealment | Blinding | Selective outcome reporting unlikely | Other aspects which increase the risk of bias | **Risk of bias** |
|---|---|---|---|---|---|

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

| | | | | | |
|---|---|---|---|---|---|
| yes | yes | yes | unclear[2] | yes[3] | unclear |
| | | | | | **First published:** 07/2022 |

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

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[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.