Report Lynparza ® - Olaparib

Product & Mechanism of action

Substance: Olaparib

Brand Name: Lynparza

Originator/license: AstraZeneca AB

Classification: NI

ATC code: L01XK01

Orphan Status:
Eu: No
Us: No

Mechanism of action: Olaparib blocks the action of the enzyme PARP, which helps to repair damaged DNA in cells (both in normal and cancer cells) during cell division. Cancer cells with mutations such as the BRCA1 or BRCA2 rely more heavily on PARP to repair their DNA and continue dividing. Therefore, when PARP is blocked, the damaged DNA in cancer cells cannot be repaired, and, as a result, the cancer cells die [1].

Authorized indications Licensing status

Authorized Indication:
EMA: olaparib 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 [2].

Route of administration: OS

Licensing status
EU CHMP P.O. date: 23/06/2022
EU M.A. date: /
FDA M.A. date: 11/03/2022

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: Yes

ABBREVIATIONS:
AML: acute myeloid leukemia
AE: adverse event
BID: twice a day
CI: confidence interval
CMF: Cyclophosphamide/methotrexate/5-fluorouracil
ESMO: European Society for Medical Oncology
HR: hazard ratio
M.A.: marketing authorization
MDS: myelodysplastic syndrome
Yrs: years
P: p value
PARP: human poly ADP ribose polymerase
PBO: placebo
P.O.: positive opinion
Pts: patients

Essential therapeutic features

Summary of clinical EFFICACY:
OlympiA (NCT02032823) is a phase III, randomised, double-blind, parallel group, placebo-controlled, multi-center study to assess the efficacy and safety of olaparib vs PBO as adjuvant treatment. Pts ≥18 yrs (N=1.836, including 6 men) were randomly assigned in a 1:1 ratio to receive olaparib (300 mg) or matching PBO tablets BID for 52 weeks.
The primary end-point was invasive disease–free survival, that was defined as the time from randomization until the date of first occurrence of one of the following events: ipsilateral invasive breast tumor, locoregional invasive disease, distant recurrence, contralateral invasive breast cancer, second primary invasive cancer, or death from any cause.
Invasive disease–free survival was significantly longer among pts assigned to receive olaparib than among those assigned to receive PBO (HR, 0.58; 99.5% CI, 0.41-0.82; P<0.001) [3].

Summary of clinical SAFETY:
A total of 1,815 pts (911 in the olaparib group and 904 in the PBO group) were included in the safety analysis. AEs that occurred in at least 10% of the pts in olaparib group were: nausea, fatigue, anemia, vomiting, headache, diarrhea, decreased neutrophil count, decreased white-cell count, decreased appetite, dysgeusia, dizziness, arthralgia.
AE leading to death were cardiac arrest in olaparib group and AML and ovarian cancer in 1 patient each in the PBO group [3].

Table 1: Summary of clinical safety

	Any grade AEs	SAEs	AE of special interest			AE leading to death
			MDS or AML	Pneumonitis	New primary cancer	
Olaparib N. pts (%)	835 (91%)	79 (9%)	2 (0.2%)	9 (1%)	19 (2.1%)	1 (0.1%)
Placebo N. pts (%)	753 (83.3%)	76 (8%)	3 (0.3%)	11(1.2%)	32 (3.5%)	2 (0.2%)

Ongoing studies:
- ***For the same indication:*** Yes [4].
- ***For other indications:*** Yes [4].

Discontinued studies (for the same indication): Yes [4].

References:
[1]. https://www.ema.europa.eu/en/medicines/human/EPAR/lynparza
[2]. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/lynparza-1
[3]. https://www.nejm.org/doi/full/10.1056/NEJMoa2105215
[4]. https://adisinsight.springer.com/drugs/800024096
[5]. https://gallery.farmadati.it/Home.aspx
[6]. https://www.aiom.it/wp-content/uploads/2021/10/2021_NumeriCancro_web.pdf
[7]. https://www.annalsofoncology.org/article/S0923-7534(19)31287-6/pdf
[8]. https://www.clinicaltrials.gov/

NHS impact

Cost of therapy:
56 coated tablets of olaparib 150 mg cost € 2,441.06 (ex-factory price) [5].

Epidemiology:
In Italy breast cancer is the most common cancer, with 55,000 new diagnosis estimated for 2020. The presence of a mutation BRCA germline is detected in approximately 5% of the pts [6].

POSSIBLE PLACE IN THERAPY
ESMO clinical practice guideline recommends chemotherapy. The most frequently used regimens contain anthracyclines and/or taxanes, although in selected pts CMF may still be used. Four cycles of doxorubicin and cyclophosphamide (AC) are considered to have equal efficacy to six cycles of CMF [7].

OTHER INDICATIONS IN DEVELOPMENT:
(phase III): Colorectal cancer, Fallopian tube cancer, Non-small cell lung cancer, Ovarian cancer, Pancreatic cancer, Peritoneal cancer, Prostate cancer, Small cell lung cancer, Squamous cell cancer [4].

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: Yes [4].

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION
Gedatolisib + Talazoparib (NCT03911973); Talazoparib (NCT02401347); Fluzoparib +/- Apatinib (NCT04296370) [8].

*Service reorganization: No
*Possible off label use: Yes

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