NCPE Assessment

Technical Summary

Olaparib (Lynparza®)

HTA ID:23029

June 2025

Applicant: AstraZeneca

Olaparib in combination with abiraterone and prednisone or prednisolone for the treatment of adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of olaparib (Lynparza®) in combination with abiraterone and prednisone or prednisolone for the treatment of adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.

Following assessment of the Applicant's submission, the NCPE recommends that olaparib (Lynparza®), for this indication, not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (AstraZeneca) Health Technology Assessment of olaparib (Lynparza®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

The Applicant (AstraZeneca) submitted a dossier investigating the clinical effectiveness, cost-effectiveness, and budget impact of olaparib in combination with abiraterone and predniso(lo)ne (ola+abi) for the treatment of adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated. The Applicant is seeking reimbursement for olaparib, for this indication, under the High-Tech Drug Arrangement.

Olaparib is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), and has been shown to inhibit tumour growth either as a standalone treatment or in combination with established chemotherapies or new hormonal agents such as abiraterone. The recommended dose of olaparib is 300mg (i.e. two 150mg tablets) twice daily, taken in combination with abiraterone 1,000 mg orally once daily and predniso(lo)ne 5 mg orally twice daily. It is recommended that patients receive ola+abi until disease progression or unacceptable toxicity occurs.

In line with current standard of care in Ireland, the proposed comparators are abiraterone in combination with predniso(lo)ne, and enzalutamide monotherapy. Subpopulations of interest include patients with mutations in genes involved in homologous recombination repair (HRRm), particularly those with the breast cancer susceptibility genes (BRCAm). Unlike BRCAm, HRRm is not currently routinely tested in this patient population in Ireland. In the subpopulation with BRCAm olaparib monotherapy, and niraparib in combination with abiraterone (nira+abi) and predniso(lo)ne are also relevant comparators.

1. Comparative effectiveness of olaparib in combination with abiraterone and predniso(lo)ne

The PROpel trial is the pivotal trial supporting the regulatory approval of ola+abi for this indication. PROpel is a phase III, international, double-blind, randomised, placebo-controlled trial designed to evaluate the safety and efficacy of ola+abi versus placebo in combination with abiraterone (pbo+abi) in patients with previously untreated mCRPC eligible for treatment with abiraterone. Abiraterone was given in combination with predniso(lo)ne in

both treatment arms. The generalisability of the trial population to the patient population in Ireland is unknown, as the trial did not require chemotherapy to be "not clinically indicated" for patients. Also, unlike current clinical practice in Ireland, patients previously treated with abiraterone were excluded. A total of 796 patients were randomised (ola+abi n=399; pbo+abi n=397). Approximately, 28.4% of patients were classified as HRRm, with 10.7% having a BRCAm. Results were presented for the primary (DCO1) and final (DCO3) analyses. Median follow-up was 19.3 and 36.5 months for DCO1 and DCO3, respectively. The PROpel trial met its primary endpoint of investigator-assessed radiological progression-free survival (rPFS-INV) in the intention to treat (ITT) population, showing a statistically significant benefit with ola+abi compared to pbo+abi (rPFS-INV hazard ratio (HR) of 0.66, 95% CI 0.54 to 0.81). The PROpel trial was not powered to demonstrate statistically significant differences in overall survival (OS) between treatment arms. At the final pre-specified analysis for OS, data were 47.9% mature and indicated a numerical (but not statistically significant) improvement with ola+abi, in the ITT population (OS HR of 0.81, 95% CI 0.67 to 1.00). Subgroup analysis indicated that benefits in the HRRm subgroup were more pronounced, particularly in the BRCAm subgroup. An rPFS-INV HR of 0.51 (95% CI 0.36 to 0.70), and an OS HR of 0.66 (0.45, 0.95) were reported for the HRRm subgroup (DC03). An rPFS-INV HR of 0.23 (95% CI 0.12 to 0.43), and an OS HR of 0.29 (95% CI 0.14 to 0.56) were reported for the BRCAm subgroup. In the non-BRCAm subgroup an rPFS HR of 0.89 (95% CI 0.70 to 1.12) (DCO1) and an OS HR of 0.91 (95% CI 0.73 to 1.13) (DCO3) were reported. Notwithstanding the potential limitations of ad-hoc subgroup analyses, the considerable differences between the ITT results and the BRCAm results suggests that the benefits with ola+abi may be driven by the small subgroup of patients with a BRCAm. The majority of the eligible patient population in Ireland is expected to be non-HRRm subgroup, and the benefits of ola+abi in these patients, notably for OS, appears to be less, but remains uncertain.

A direct comparative trial was only available to provide comparative effectiveness evidence for ola+abi versus abiraterone. Indirect comparison methods are required to inform the comparisons with enzalutamide in the full population, and with olaparib monotherapy and nira+abi in the BRCAm subpopulation. Full details of a network meta-analysis (NMA) were provided for the enzalutamide comparison, however heterogeneity in the trials included in the NMA compromises the reliability of the results. No comparative effectiveness evidence for olaparib monotherapy in the BRCAm subpopulation was provided by the Applicant. A

summary of an NMA comparing ola+abi and nira+abi was provided for the BRCAm subpopulation, based on a conference abstract. However, details of the NMA methods were not provided and the robustness of the NMA and the reliability of its findings could not be assessed.

2. Safety of olaparib in combination with abiraterone and predniso(lo)ne

Overall, the safety profile of ola+abi in the PROpel trial is consistent with previous data from olaparib monotherapy. The most frequently reported adverse events (AEs) in the ola+abi arm were anaemia, fatigue or asthenia, and nausea. The most common serious adverse events (SAEs) in the ola+abi arm, reported at an incidence ≥ 2%, were anaemia (5.8%), pulmonary embolism (3.8%), COVID-19 (3.8%), pneumonia (2.8%), and urinary tract infection (2.3%). Compared to pbo+abi, ola+abi has a 10% or higher incidence of the following AEs: anaemia (49.7% vs 17.7%), nausea (30.7% vs 14.4%), diarrhoea (20.6% vs 10.6%), and decreased appetite (16.6% vs 7.8%).

3. Cost effectiveness of olaparib in combination with abiraterone and predniso(lo)ne

Methods

The Applicant submitted a cost-utility analysis using a partitioned survival model developed in Microsoft Excel®. The model included three mutually exclusive health states: progression-free (PF), progressed disease (PD), and death. The model assumed a cycle length of one month and a lifetime horizon. The time to treatment discontinuation (TTD), rPFS, and OS of ola+abi and abiraterone were extrapolated using parametric survival models fitted to time-to-event data from the PROpel trial.

The Applicant provided separate cost-effectiveness analyses for the full population and for the HRRm subpopulation. Abiraterone is considered to be the primary comparator for the purposes of the cost-effectiveness analysis in the full population, and cost-effectiveness results for this comparison only are presented for this population. The NCPE Review Group requested additional analysis in a number of relevant subpopulations. Comparisons with abiraterone, enzalutamide and nira+abi were presented in the relevant subpopulations. A comparison against olaparib monotherapy in the BRCAm subpopulation was not provided. This is considered to be a major limitation of the submission. This subpopulation may be of

greatest relevance, in Ireland, given the current testing landscape. Also, clinical opinion has identified an unmet need in patients with a BRCAm due to more aggressive disease and poor prognosis.

The short duration of follow-up relative to the model time horizon results in considerable uncertainty in the survival extrapolations derived from the PROpel trial. In both the subpopulations with HRRm and BRCAm, the Applicant's chosen distribution for the extrapolation of long-term OS, predicted longer OS for ola+abi arm in the modelled subpopulation than in the modelled full population. This was considered by the Review Group to be implausible, given that patients with mCRPC with these mutations are recognised to have more severe disease than patients without. Alternative distributions were selected by the Review Group to model OS in the subpopulation models, based on statistical fit and clinical plausibility of landmark survival over time. The Applicant's choice of distributions to model TTD were also considered to be inappropriate, leading to implausible divergence between the PFS and TTD. The Review Group selected alternative TTD distributions, of the same functional form as the selected PFS distribution, which also had a better statistical fit to the observed data.

Health-related quality of life utility estimates for the PF and PD health states were informed by the PROpel trial in the Applicant's model. The Review Group had concerns that the utility for the progressed disease health state is very uncertain, appearing implausibly high for a progressed advanced cancer health state, relative to the PF health state utility and that of the general population. In addition, fewer observations were used to derive the PD utility value compared to the PF health state utility value, and these data were only collected in the first 12-weeks post-progression. The Review Group considered that an alternative source of utility data for PD, based on a large observational study, conducted across Europe, provided a more plausible value for the PD health state utility and applied this value in the NCPE Adjusted base case. A utility adjustment accounting for age-related utility decrements was inappropriately omitted by the Applicant. This adjustment was included in the NCPE's adjusted cost-effectiveness model for ola+abi versus abiraterone, among the other adjustments including alternative TTD extrapolations (in all populations), alternative OS extrapolations (in the subpopulation analyses) and source of PD utility data.

Direct medical costs were included for drug acquisition (including administration), disease management, subsequent treatments, biomarker testing and AEs. A one-time end-of-life cost was applied. Irish costs were applied where available.

Results

Due to uncertainty in the assumptions used in the submitted cost-effectiveness model, the Review Group made several changes to the Applicant's base case, based on more plausible alternative assumptions in an NCPE-adjusted base case, as described in the previous section. The cost-effectiveness results arising from the Applicant's and the NCPE-adjusted base-case analyses are presented in Tables 1 and 2. Results are presented only for the comparisons of ola+abi with abiraterone, due to a lack of robust comparative-effectiveness evidence compared with enzalutamide or nira+abi, and no comparison with olaparib monotherapy.

Table 1: Applicant base case incremental cost-effectiveness results [a, b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Full population					
Olaparib + abiraterone	210,731	3.75	-	-	-
Abiraterone	70,830	2.57	139,901	1.17	119,124
HRRm population[c]					
Olaparib + abiraterone	230,846	3.93	-	-	-
Abiraterone	67,356	2.05	163,490	1.88	87,091
BRCAm population[d]					
Olaparib + abiraterone	346,390	5.56	-	-	-
Abiraterone	64,755	2.02	281,636	3.54	79,628

Abbreviations: *BRCA*m: breast cancer susceptibility gene mutated; HRRm: homologous recombination repair pathway gene mutation; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; QALY: quality adjusted life year. Costs and outcomes discounted at 4%.

[a] Corresponding probabilistic ICERs using 1,000 iterations:
Full population; vs abiraterone = €119,174/QALY
HRRm population; vs abiraterone = €85,197/QALY
BRCAm population; vs abiraterone = €83,016/QALY
Figures in the table are rounded, and so calculations may not be directly replicable

[b] A commercial-in-confidence PAS is in place for olaparib and abiraterone, not included in this table.

Table 2: NCPE adjusted base case incremental cost-effectiveness results [a, b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Full population					
Olaparib + abiraterone	244,430	3.42			
Abiraterone	73,423	2.36	171,008	1.06	161,651
HRRm population					
Olaparib + abiraterone	260,796	3.01			
Abiraterone	69,173	1.96	191,623	1.06	181,046
BRCAm population					
Olaparib + abiraterone	345,498	4.39			
Abiraterone	64,078	1.59	281,419	2.80	100,585

Abbreviations: *BRCA*m: breast cancer susceptibility gene mutated; HRRm: homologous recombination repair pathway gene mutation;

ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; QALY: quality adjusted life year Costs and outcomes discounted at 4%.
[a] Corresponding probabilistic ICERs using 1,000 iterations:
Full population; vs abiraterone = €159,199/QALY
HRRm population; vs abiraterone = €177,649/QALY
BRCAm population; vs abiraterone = €98,792/QALY
Figures in the table are rounded, and so calculations may not be directly replicable
[b] A commercial-in-confidence PAS is in place for olaparib and abiraterone, not included in this table.

The results in the HRRm and BRCAm subpopulations are particularly uncertain, given the very small patient numbers contributing to the assessment of efficacy, and the absence of a robust comparison versus olaparib monotherapy, or nira+abi. Inconsistencies in the relative cost-effectiveness results across populations, between the Applicant and NCPE-adjusted base case, highlight the uncertainty in the underlying clinical evidence results and corresponding long-term survival estimates. Results should be interpreted with caution.

Sensitivity analysis

Sensitivity analyses indicated that the main drivers of cost-effectiveness related to the selected parametric distributions for OS and TTD and the health-related quality of life utility in the PD health state. A price-ICER analysis, under the NCPE-adjusted base case assumptions, was conducted for ola+abi versus abiraterone in the full population. The analysis indicated that a reduction of approximately 79% and 95% in the price-to-wholesaler (PtW) of olaparib would be required to meet the €45,000 per QALY threshold, and €20,000 per QALY threshold, respectively.

4. Budget impact of olaparib in combination with abiraterone and predniso(lo)ne

The price-to-wholesaler (PtW) of olaparib is €2,445.81 for one pack of olaparib 150mg tablets (pack size 56). The estimated total cost of ola+abi to the HSE per patient per treatment course is €221,244 (including VAT), assuming a mean treatment duration for olaparib and abiraterone of 34.99 months and 36.22 months, respectively, based on TTD derived from the cost-effectiveness model. The Applicant presented budget impact analyses (BIAs) for the full population and the HRRm subpopulation. The NCPE Review Group also requested a BIA in the BRCAm subpopulation. The Applicant used several sources to inform the eligible patient estimates, including National Cancer Registry of Ireland (NCRI) data, the published literature, and clinical opinion. Many of the inputs are uncertain, leading to considerable uncertainty associated with budget impact estimates. The Applicant estimated that 29 patients in the full population will receive treatment in year 1, increasing to 75 in

year 5. In the HRRm and BRCAm subpopulations, patient numbers in year 5 are predicted to be 31 and 10, respectively.

The five-year cumulative net drug budget impact for ola+abi was estimated by the Applicant to be €25.4 million (VAT not applicable for oral medicines) in the full population. The NCPE estimated a five-year cumulative net drug budget impact, based on a more plausible treatment duration, of €35.1 million. In the HRRm and BRCAm subpopulations, five-year cumulative net drug budget impact estimates decrease in line with patient numbers to €14.1 million and €5.6 million, respectively (based on NCPE estimates of treatment duration).

5. Patient Organisation Submission

A patient organisation submission was received from Men Against Cancer.

6. Conclusion

Ola+abi is licensed in a broad population, however comparative effectiveness and cost effectiveness are expected to vary considerably across subpopulations. A lack of comparative effectiveness evidence in the BRCAm subpopulation, in particular, compounded by very small patient numbers in the pivotal clinical trial, make cost-effectiveness results in this subpopulation highly uncertain. The NCPE recommends that olaparib (in combination with abiraterone and predniso(lo)ne) not be considered for reimbursement (for the indication under assessment) unless cost-effectiveness can be improved relative to existing treatments*

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.