Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2617

olaparib film-coated tablets (Lynparza®)

AstraZeneca UK Ltd

09 February 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

olaparib (Lynparza®) is accepted for use within NHSScotland.

Indication under review: in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.

In a phase III study, radiographic progression-free survival was significantly improved with the addition of olaparib to abiraterone plus prednisone or prednisolone compared with the addition of placebo in patients with mCRPC who had received no previous systemic therapy for metastatic disease.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

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 the growth of selected tumour cells. It exploits deficiencies in DNA repair pathways to preferentially kill cancer cells with these deficits compared to normal cells.[1, 2]

When used in combination with abiraterone plus prednisone or prednisolone for mCRPC, the recommended dose of olaparib is 300 mg orally twice daily; the concomitant recommended dose of abiraterone is 1,000 mg orally once daily and of prednisone or prednisolone is 5 mg orally twice daily. It is recommended that treatment is continued until progression of the underlying disease or unacceptable toxicity. Olaparib has also been accepted for use in NHSScotland for use 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. [1]

1.2. Disease background

Prostate cancer is the most common cancer in men. In the advanced stages, the majority of patients develop mCRPC. The main metastatic site for prostate cancer is bone and this can cause substantial morbidity in patients including bone pain, skeletal-related events, spinal cord compression and pathological fractures. Patients may also experience symptoms associated with problems in urinating and fatigue.[2]

1.3. Treatment pathway and relevant comparators

Local or locally advanced prostate cancer is treated with surgery or radiotherapy followed by androgen deprivation therapy which aims to suppress androgen levels either by surgery (orchidectomy) or with hormonal therapy such as luteinising hormone releasing hormone (LHRH) agonists and antagonists and androgen receptor inhibitors. However, if the cancer becomes castration resistant, with progression despite castration levels of testosterone, further treatment can be considered. Clinical guidelines have recommended treatment with the androgen targeted agents, abiraterone or enzalutamide, for patients with asymptomatic or mildly symptomatic mCRPC who are chemotherapy naïve, or unsuitable for docetaxel or cabazitaxel. Radium-223 can be considered for patients with symptomatic bone metastases without visceral metastases. However, the optimal approach for sequencing or combining currently available treatments remains unclear; treatment choice is based on disease characteristics, previous treatment, patient co-morbidities, performance status and preference.

Abiraterone (with prednisone or prednisolone) and enzalutamide are both licensed and accepted for use by SMC in patients with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (SMC873 and SMC1066). Enzalutamide is also licensed for adult men with high-risk non-metastatic castration-resistant prostate cancer but was not recommended for use by SMC (SMC2195). [2-5]

Abiraterone, enzalutamide, apalutamide and darolutamide are accepted for use at earlier stages of prostate cancer in NHSScotland[3, 4 6-9] There is currently no evidence to support the sequential use of abiraterone and enzalutamide.

Clinical experts consulted by SMC considered the relevant treatment comparators for this submission are abiraterone (plus prednisone or prednisolone) or enzalutamide.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Olaparib received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway.

Eligibility for a PACE meeting

Olaparib meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of olaparib in combination with abiraterone plus prednisolone for the treatment of mCRPC comes from the PROpel study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[2, 10, 11]

Criteria	PROpel
Study design	A double-blind, randomised, multicentre, phase III study
Eligible patients	- patients aged ≥18 years with histologically or cytologically confirmed prostate adenocarcinoma - metastatic status defined as at least one documented metastatic lesion on either a bone or CT/MRI scan - documented evidence of progressive disease, defined as one or more of the following whilst patient was taking ADT: - PSA progression (at least two rising PSA levels with ≥1 week interval between) - soft-tissue disease progression as per RECIST 1.1 criteria. - bone progression (at least two new lesions on a bone scan [PCWG-3 criteria]). - ongoing ADT with GRHA or bilateral orchiectomy, with serum testosterone <50 nanograms/dL (<2.0 nanomol/L) in previous 28 days. Patients receiving ADT at study entry continued ADT during the study - had not received any cytotoxic chemotherapy, new hormonal agent or other systemic treatment for mCRPC. Previous treatment with new hormonal agents (except abiraterone) was allowed provided there was no PSA or clinical or radiological progression during treatment and that treatment was stopped ≥12 months before randomisation). - ECOG performance status of 0 or 1. - life expectancy of ≥ 6 months
Treatments	Eligible patients were randomised equally to receive: - olaparib 300 mg orally twice daily plus abiraterone 1,000 mg orally once daily plus prednisone or prednisolone 5 mg orally twice daily or - placebo orally twice daily plus abiraterone 1,000 mg orally once daily plus prednisone or prednisolone 5 mg orally twice daily. Treatment was continued until radiological progression or unacceptable toxicity.

Randomisation	Randomisation was stratified according to metastases (bone only, visceral or other) and docetaxel treatment at mHSPC stage (yes or no).
Primary outcome	rPFS, defined as time to radiographic progression (investigator assessed using RECIST v1.1 for soft tissue lesions and PCWG3 criteria for bone lesions) or death due to any cause.
Secondary outcomes	- OS, defined as the time from randomisation to death from any cause (key secondary outcome) - TFST, defined as time to first subsequent anticancer therapy or death, defined as time from randomisation to start of first subsequent anticancer therapy or death from any cause. - TTPP, defined as time from randomisation to pain progression based on BPI-SF "worst pain in 24 hours" and opiate analgesic use. - Time to SSRE defined as the time from randomisation to first symptomatic skeletal-related event (defined as radiation to prevent or relieve skeletal symptoms, new symptomatic bone fracture, spinal compression or orthopaedic surgical intervention for bone metastases) - PFS2 defined as the time from randomisation to second progression on next-line
Statistical analysis	A hierarchical testing procedure was applied to the primary and key secondary outcomes of the study with no formal testing after the first non-significant outcome in the hierarchy.
CT=computed tomography; MRI=magnetic resonance imaging; ADT= androgen deprivation therapy; GRHA=gonadotropin-releasing hormone analogue; mHSPC=metastatic hormone sensitive prostate cancer; PSA=prostate specific antigen; ECOG=Eastern Co-operative Oncology Group; rPFS=radiographic progression free survival; RECIST= Response Evaluation Criteria in Solid Tumours; PCWG3= Prostate Cancer Working Group; OS=overall survival; TFST=time to first subsequent anticancer therapy or death; TTPP=time to pain progression; BPI-SF=brief pain inventory-short form; SSRE=symptomatic skeletal-related event; PFS2=time from randomisation to second progression or death.	

At the time of the primary radiographic progression-free survival (rPFS) analysis (data cut-off 30 July 2021), median rPFS was significantly improved by the addition of olaparib. Results for the key secondary outcome of overall survival (OS) were immature at this time but did not reach statistical significance at the time of the final OS analysis (data cut-off 12 October 2022). Details of relevant study results are presented in Table 2.2.

Table 2.2: Results for the primary and relevant secondary outcomes in the PROpel study (ITT population)[2, 10-14]

	Primary rPFS analysis (30 July 2021)		**Final OS analysis (12 October 2022)**	
	Olaparib plus abiraterone (n=399)	**Placebo plus abiraterone (n=397)**	**Olaparib plus abiraterone (n=399)**	**Placebo plus abiraterone (n=397)**
Primary outcome: rPFS by investigator				
Median duration of follow-up in patients with censored data, months	19.3	19.2	32.5	33.0
Number of patients with a PFS event	168	226	219	277
Median PFS, months	24.8	16.6	25.0	16.5
Hazard ratio (95% CI)	0.66 (0.54 to 0.81) p<0.001		0.68 (0.57 to 0.81)	
KM estimates progression-free at 12 months	72%	63%	-	-

KM estimates progression-free at 24 months	51%	34%	-	-
Key secondary outcome: OS				
Median duration of follow-up in patients with censored data, months	-	-	36.6	36.5
Number of deaths	107	121	176	205
Median OS, months	NE	NE	42.1	34.7
Hazard ratio (95% CI)	0.86 (0.66 to 1.21), p=0.29		0.81 (0.67 to 1.00), p=0.054	
KM estimates of survival at 24 months	-	-	70%	67%
KM estimates of survival at 36 months	-	-	57%	50%
Time to SSRE				
Number of events	37	47	*	*
Median time to SRE	NE	NE	NE	NE
Hazard ratio (95% CI)	0.72 (0.47 to 1.11)		0.82 (0.55 to 1.22)	

rPFS=radiographic progression free survival; CI=confidence interval; KM=Kaplan Meier; NE=not estimated; OS=overall survival; SSRE=symptomatic skeletal-related event
**results for the number of SSRE events at the 12 October 2022 cut-off were considered confidential by the company*

Additional descriptive secondary outcomes, time to first subsequent anticancer therapy or death (TFST), time to pain progression (TTPP) and time to second progression or death (PFS2), numerically favoured olaparib over placebo, with the exception of TTPP.[2, 10, 11]

Subgroup analyses of rPFS according to aggregate analysis based on circulating tumour DNA and tissue testing, found a larger treatment effect in patients with homologous recombination repair (HRR) mutation (n=226; HR 0.50 [95% CI 0.34 to 0.73]) compared with those without HRR mutation (n=552; HR 0.76 [95% CI 0.60 to 0.97]). The treatment effect for rPFS was also larger in patients with a BRCA mutation (n=85; HR 0.23 [95% CI 0.12 to 0.43]) compared with those without (n=693; HR 0.76 [95% CI 0.61 to 0.94]). Similarly, subgroup analyses of OS at the final data cut found a larger treatment effect in patients with HRR mutation (226; HR 0.66 [95% CI 0.45 to 0.95]) compared with those without HRR mutation (n=552; HR 0.89 [95% CI 0.70 to 1.14]) and with a BRCA mutation (n=85; HR 0.29 [95% CI 0.14 TO 0.56] compared with those without (n=693; HR 0.91 [95% CI 0.73 to 1.13]).[2, 10, 11]

Following confirmed radiographic progression, crossover was not allowed but patients could receive subsequent anticancer therapy at the discretion of the investigator. By the time of the final OS analysis (data cut-off 12 October 2022), 45% of patients in the olaparib group and 54% of patients in the placebo group had received subsequent anticancer therapy. This was mainly docetaxel (24% of olaparib and 36% of placebo patients), cabazitaxel (11% and 16% respectively), enzalutamide (9.8% and 12% respectively) and abiraterone (5.8% and 4.8% respectively).[10]

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the Functional Assessment of Cancer Therapy-Prostate Cancer (FACT-P) questionnaire (this included the FACT-P total score and domains for physical well-being, social/family well-being, emotional well-being, functional well-being, prostate cancer subscale), the FACT-general (FACT-G) total score, the Trial Outcome Index (TOI) and the Functional Assessment of Prostate Cancer Symptoms Index 6 (FAPSI-6). The severity of pain and its impact were assessed using the Brief Pain Inventory Short Form (BPI-SF) questionnaire and general health status was measured using the European Quality of Life (EQ-5D-5L). These instruments were used at screening, every 4 weeks until week 52 and then every 8 weeks until treatment discontinuation or 12 weeks after progressive disease.[10, 11]

Available data at the primary analysis of rPFS (data cut-off 30 July 2021) and the final OS analysis (12 October 2022), suggested that the HRQoL results for the olaparib versus placebo groups were similar.[2, 11, 12]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

The submitting company conducted a feasibility assessment of indirect treatment comparisons (ITCs) between olaparib plus abiraterone plus prednisolone versus abiraterone plus prednisolone and versus enzalutamide in patients with mCRPC using two outcomes (PFS and OS). However, differences between the studies in terms of control arms (placebo and placebo plus prednisolone) could potentially affect PFS and the submitting company considered that it was not possible to indirectly compare on this outcome. The submitting company considered that there was no evidence to suggest that prednisolone has an effect on OS and in order to construct a network from the available studies, it was assumed that prednisolone was of equivalent efficacy to placebo for this outcome. Network meta-analysis (NMA) results indicated that enzalutamide is similar to abiraterone (plus prednisolone) for OS with a hazard ratio close to 1, however, interpretation is limited by heterogeneity across the studies included in the network. For the base case analysis in the economics, it was assumed that enzalutamide was equivalent in efficacy to abiraterone plus prednisolone and the relative treatment effect of olaparib plus abiraterone plus prednisolone versus abiraterone plus prednisolone was used as a proxy for olaparib plus abiraterone plus prednisolone versus enzalutamide. Clinical experts consulted by SMC felt that this was a reasonable assumption. Scenario analysis in the economics used the calculated hazard ratios from the NMA.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In the PROpel study at data cut-off 12 October 2022, the median duration of treatment in the olaparib group was 18.5 months for olaparib and 20.1 months for abiraterone and in the placebo group was 15.7 months for both placebo and abiraterone. In the olaparib and placebo groups respectively, patients reporting a grade 3 or higher adverse event (AE) were 56% versus 43%, patients with a reported serious AE were 40% versus 32%, patients with a dose reduction due to treatment emergent AEs were 23% versus 6.1%, the proportion of AEs that led to dose interruptions were 36% versus 24% and patients discontinuing therapy due to an AE was 17% (olaparib) versus 8.6% (placebo).[10, 14]

At data cut-off 12 October 2022, the most frequently reported treatment- emergent AEs of grade 3 or higher in the olaparib group versus the placebo group were: anaemia (16% versus 3.3%), hypertension (3.8% versus 4.5%), COVID-19 (3.8% versus 2.0%), urinary tract infection (2.5% versus 1.0%), fatigue or asthenia (2.5% versus 1.5%), vomiting (1.5% versus 0.3%), diarrhoea (1.3% versus 0.3%), back pain (1.0% versus 1.5%) and decreased appetite (1.0% versus 0%).[10]

There were several AEs of special interest reported in the PROpel study. These included two cases of myelodysplastic syndrome reported in the olaparib group; 18 cases of new primary malignancy in the olaparib group and 14 cases in the placebo group; and pneumonitis (which comprised interstitial lung disease, pneumonitis and radiation pneumonitis) which occurred in five patients in the olaparib group and three patients in the placebo group.[10]

Overall, the safety profile of olaparib in the PROpel study was similar to that of previous studies of olaparib in other indications. The only new adverse event identified for olaparib was venous thromboembolism (VTE) (proportion of patients with at least one AE of embolic and thrombotic venous AE: 8.5% versus 4.0%). Although the combined treatment of olaparib plus abiraterone represents a heavier treatment regimen for patients with mCRPC compared with abiraterone alone, the toxicity was most often manageable with dose interruptions, reductions, and standard supportive treatments.[10]

SPC provides details of risk and management of haematological toxicities, myelodysplastic syndrome/acute myeloid leukaemia, venous thromboembolic events and pneumonitis.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- The main evidence comes from the randomised, double-blind, phase III study, PROpel. The control group, placebo plus abiraterone (plus prednisone or prednisolone), can be considered a relevant comparator. Compared with placebo, the addition of olaparib to abiraterone plus prednisolone was associated with a rPFS benefit of 8.2 months at the primary analysis and this was considered clinically relevant. Although rPFS was investigator-assessed, results were similar when assessed independently.[2, 11]
- Despite a higher incidence of AEs in patients who received olaparib, the HRQoL outcomes indicated similar results suggesting that there was no detrimental effect on quality of life.[2, 10, 11]

4.2. Key uncertainties

- Although the addition of olaparib to abiraterone plus prednisolone significantly improved rPFS, there was no significant improvement in OS at any data cut-off. At the final OS analysis, the improvement in OS of 7.4 months was not enough to meet the pre-specified level of significance. Final OS results may be confounded by the use of subsequent anticancer therapy (45% of patients in the olaparib group and 54% of patients in the placebo group).[10]
- Additional secondary outcomes, with the exception of TTPP, numerically favoured the addition of olaparib to abiraterone plus prednisolone but these were not included in the hierarchical testing strategy and are considered descriptive only. The number of observed events for TTPP was small.[2, 10, 11]

- Although the treatment benefits on rPFS and OS generally consistently favoured adding olaparib to abiraterone plus prednisolone, the size of the benefit was smaller in patients without HRR or BRCA mutations compared with those with. However, both tissue and blood samples were collected at baseline for retrospective classification of mutations and analyses according to mutation subgroups were performed in a post hoc manner. In addition, the study was not powered for subgroup analysis and these results should be interpreted with caution. [1, 2, 10, 11]

- With the availability of abiraterone and enzalutamide for earlier use in the hormone-sensitive or non-metastatic CRPC setting, the proportion of patients who remain eligible to receive abiraterone (and hence olaparib in combination with abiraterone) at this later mCRPC stage is likely to be decreasing. There is no evidence to support the use of olaparib plus abiraterone plus prednisolone in patients whose disease had progressed despite prior treatment with abiraterone or enzalutamide. In PROpel, patients could have received previous NHA (other than abiraterone) if it had been discontinued at least one year beforehand; only one patient had received prior treatment with enzalutamide.[2, 11]

- In PROpel, olaparib plus abiraterone plus prednisone or prednisolone was compared with abiraterone plus prednisone or prednisolone and there are no direct randomised data compared with enzalutamide. An exploratory NMA suggested that abiraterone plus prednisone or prednisolone was of equivalent efficacy to enzalutamide however this relied on several underlying assumptions.

4.3. Innovative Licensing and Access Pathway (ILAP) and ongoing studies

SMC can consider the interim acceptance decision option when encountering clinical uncertainty for medicines with an Innovation Passport. Since results of the final OS analysis of the key PROpel study have now been published and no further evidence is expected, the interim decision option is unlikely to be useful on this occasion.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that olaparib is a therapeutic advancement offering a new combination of therapy with improved progression-free survival. Clinical experts considered that the place in therapy of olaparib is in patients who have not received prior NHA therapy and noted the benefit is greatest in those with relevant disease mutations.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **olaparib**, as an **orphan-equivalent and end of life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Prostate cancer is the most common cancer in men in Scotland, accounting for a quarter of all cancers. Metastatic castration-resistant prostate cancer (mCRPC) is an incurable illness which is associated with significant morbidity and impacts the physical and mental well-being of patients.

- Controlling disease progression and improving overall survival, whilst not adversely affecting quality of life are key goals of treatment for mCRPC. There is an unmet need for further treatment options to help achieve this goal; to tailor therapy by providing the optimal treatment for the individual patient, while allowing them to maintain daily functioning.
- The addition of olaparib to abiraterone would provide a further treatment option for patients with mCRPC and may relieve the psychological distress for patients and their families of exhausting treatment options. It may delay disease progression, control symptoms and delay the need for further treatments. This may allow patients to feel well, maintaining their daily functioning and independence, relieving the burden of disease on patients, families and carers, allowing them to lead more normal lives.
- Olaparib would be an additional oral treatment which would generally be convenient for patients. There would be limited service implications for delivery but more frequent clinic visits may be required to monitor treatment and manage side effects. The PACE participants highlighted that it was important to target treatment to those patients considered most likely to benefit (that is, those with a BRCA mutation) and minimise unnecessary toxicity in those who would be unlikely to benefit.
- The PACE participants noted that very few patients would not have received a NHA by the time their disease becomes castration resistant, making them eligible for this olaparib plus abiraterone combination therapy. By targeting olaparib treatment to those patients considered most likely to benefit (that is, those with a BRCA mutation), the number of patients becomes even smaller.

Additional Patient and Carer Involvement

We received patient group submissions from Prostate Cancer UK, Prostate Cancer Research and Prostate Scotland. All three organisations are registered charities. Prostate Cancer UK has received less than 1% pharmaceutical company funding in the past two years, including from the submitting company. Prostate Cancer Research has received 8% pharmaceutical company funding in the past two years, with none from the submitting company. Prostate Scotland has not received any pharmaceutical company funding in the past two years. Representatives from Prostate Cancer UK and Prostate Scotland participated in the PACE meeting. The key points of the submissions from all three organisations have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	Lifetime horizon 30 years
Population	Adult patients with mCRPC in whom chemotherapy is not clinically indicated

Comparators	1) Abiraterone (with prednisone or prednisolone) 2) Enzalutamide
Model description	A partitioned survival model was presented using three mutually exclusive health states (progression free (PF), progressed disease (PD), and death), applying a 1-month cycle length. All patients entered the model in the PF health state and were assumed to initiate first line treatment for mCRPC.
Clinical data	OS, rPFS and time to treatment discontinuation (TTD) for olaparib in combination with abiraterone and the abiraterone comparator were modelled using patient-level data from the PROpel study.[2, 10, 11] The company did not identify any direct randomised data comparing olaparib plus abiraterone with enzalutamide. An NMA was conducted which suggested no difference in OS between abiraterone and enzalutamide. A similar approach to rPFS was explored, but differences between the studies in terms of a lack of common control arm led the submitting company to conclude that it was not possible to indirectly compare on this outcome, without introducing bias into the model. An assumption was made that there is equivalence between abiraterone and enzalutamide for both OS and PFS, with a hazard ratio of 1 being applied in the model. This assumption was supported by clinical opinion received by the submitting company and SMC.
Extrapolation	Based on the results of the OS from the NMA, and clinical opinion, OS, rPFS and TTD were modelled identically between abiraterone plus prednisone/prednisolone and enzalutamide. Parametric survival curves were applied to extrapolate rPFS, OS, and TTD for both arms. The company determined that the proportional hazards assumption did not hold across all outcomes and so independently fitted models were used throughout. Parametric models were selected through an assessment of visual and statistical fit, external validation, and clinical validation. In the base case model, the generalised gamma was used to extrapolate OS and rPFS for all treatment arms and a Weibull distribution was selected for all TTD curves.
Quality of life	Health related quality of life data were collected from participants of the PROpel study using the EQ-5D-5L questionnaire, then 'cross-walked' into EQ-5D-3L outputs based on the algorithm developed by Hernandez Alava et al (2017).[15] The model uses separate health state utility values for the pre-progressed and progressed health states. Adverse event disutility and skeletal related events (SRE) disutilities were applied as a one-off value at the start of the modelled period.
Costs and resource use	The economic analysis included costs associated with medicine acquisition, administration, health-state monitoring, subsequent treatments, adverse events, skeletal-related events, and end of life costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for enzalutamide and this was included in the results used for decision-making by using estimates of the comparator PAS price

6.2. Results

The base case economic results suggested that treatment with olaparib combination with abiraterone and prednisone or prednisolone was associated with higher costs and better health outcomes than enzalutamide or abiraterone and prednisone or prednisolone. The specifics of the results cannot be published due to them being classed as commercial in confidence by the company.

6.3. Sensitivity analyses

The company explored uncertainty within the modelling through probabilistic sensitivity analysis, deterministic sensitivity analysis and scenario analysis. The results of these analyses cannot be published due to them being classed as commercial in confidence by the company.

A select range of the conducted scenario analyses are presented in Table 6.2 below, inclusive of the PAS discount on olaparib only.

Table 6.2 Summary of Scenario Analysis

	Scenario description	Base case description
	Time Horizon	
1	20 years	30 years
	Abiraterone vs. enzalutamide HR	
2	PFS = 0.962 (Chowdhury et al)	HR of 1.0
3	NMA, OS fixed effects	
4	NMA, OS random effects inc. informative priors	
	OS extrapolation (both arms)	
5	Log Logistic	Generalised gamma
	PFS extrapolation (both arms)	
6	Lognormal	Generalised gamma
7	Log Logistic	Generalised gamma
	TTD extrapolation (both arms)	
8	Generalised Gamma	Weibull
	Cost inclusion	
9	Secondary therapy cost excluded	Secondary therapy cost included
10	Adverse event costs excluded	Adverse event costs included
11	Wastage excluded	Wastage included
	Utility	
12	AE disutility excluded	AE disutility included
13	SRE disutility excluded	SRE disutility included

Abbreviations: OS, overall survival; PFS, progression free survival; TTD, time to discontinuation; HR, hazard ratio; AE, adverse events; SRE, Skeletal-related events; NMA, network-meta analysis

6.4. Key strengths

The strengths in the model include the following:

- The selected comparators appeared to be the most likely medicines to be displaced in Scottish clinical practice.
- The economic model is structurally sound and costing has been comprehensive.
- Data directly comparing olaparib plus abiraterone and placebo plus abiraterone was available from the PROpel study.

6.5. Key uncertainties

The weaknesses in the model include the following:

- There is a lack of direct randomised evidence comparing olaparib plus abiraterone and enzalutamide, which was considered a relevant comparator. An assumption was made of equivalence between abiraterone and enzalutamide for both OS and PFS, with a hazard ratio of 1 being applied in the model. Deterministic scenario analysis showed that choice of

hazard ratios, particularly for PFS, were a key driver of results. However, alternative values explored in scenario analysis, which used a much smaller range of alternative values, demonstrated limited impact on the ICER. SMC clinical experts also suggested equivalence between abiraterone and enzalutamide is a reasonable assumption.

- Given the reliance on short-term study data, there is an inherent degree of uncertainty in the extrapolation of clinical outcomes, with possible plausible alternative selections leading to changes in the estimated cost-effectiveness. Alternative parametric curves to the base case had good visual and statistical fit to the study data and led to meaningful increases in the incremental cost-effectiveness ratio. However, these alternatives did not align well with clinical expectations received by the company from experts.
- As noted in the clinical case, data from the PROpel study indicated that mutation status may impact upon patient outcomes. Subgroup analysis was not provided within the economic modelling. Despite the study not being powered for subgroup analysis, meaning the economic analysis would have been associated with uncertainty, results broken down by mutations status would have been informative for discussions.

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of olaparib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as olaparib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted olaparib for use in NHSScotland.

8. Guidelines and Protocols

The European Association of Urology (EAU), European Society for Radiotherapy and Oncology (ESTRO), European Association of Nuclear Medicine (EANM), European Society of Urogenital Radiology (ESUR), International Society of Urological Pathology (ISUP) and International Society of Geriatric Oncology (SIOG) published joint guidance "Guideline on Prostate Cancer" which was last updated in March 2023.[16]

The National Institute for Health and Care Excellence (NICE) published NICE national guideline (NG131) "Prostate cancer: diagnosis and management" in May 2019 which was last updated in December 2021.[17]

The European Society for Medical Oncology (ESMO) published "Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" in June 2020.[5]

9. Additional Information

9.1. Product availability date

15 March 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
olaparib plus abiraterone plus prednisolone	**300 mg orally twice daily 1,000 mg orally once daily 5 mg orally twice daily**	**85,167**

Costs from BNF online on 1 November 2023. Costs do not take any patient access schemes or any other discounts into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimates that there will be around 25 patients eligible for treatment with olaparib in year one rising to 43 in year five. The uptake rate was estimated to be 29% in year one (7 patients) and 62% in year five (27 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 15 December 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.