

**6.08 OLAPARIB,
Tablet 100 mg,
Tablet 150 mg,
Lynparza[®],
AstraZeneca Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 85 General Schedule, Authority Required (telephone/online) listing for olaparib in combination with abiraterone for the first line treatment of metastatic castration-resistant prostate cancer (mCRPC) patients with breast cancer gene (BRCA)1/2 pathogenic variants who have not received prior treatment with a novel hormonal agent (NHA).
- 1.2 Listing was requested on the basis of a cost-utility analysis versus NHA monotherapy.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients diagnosed with metastatic castration-resistant prostate cancer (mCRPC) and confirmed BRCA1 or BRCA2 pathogenic variants who have not received prior NHA treatment
Intervention	Olaparib 300 mg (2×150 mg) twice daily (total dose 600 mg/day) in combination with abiraterone once daily plus corticosteroid (two formulations: abiraterone 1 g/day + prednisone/prednisolone 8 mg/day and abiraterone 500 mg/day + methylprednisolone 10 mg/day)
Comparator	Main comparator: NHA monotherapy with either abiraterone or enzalutamide Near market comparators: - Talazoparib 0.5 mg once daily in combination with enzalutamide 160 g once daily - Niraparib 200 mg once daily in combination with abiraterone once daily
Outcomes	OS, PFS, PROs, safety, AEs
Clinical claim	The combination of olaparib plus abiraterone demonstrates superior efficacy and inferior safety when compared to abiraterone plus placebo in NHA-naïve mCRPC patients with a confirmed BRCA1 or BRCA2 pathogenic variant.

Source: Table 1-1, p15 of the submission.

AE=adverse events; BRCA=breast cancer gene; mCRPC=metastatic castration- prostate cancer; NHA=novel hormonal agent; OS=overall survival; PFS=progression-free survival; PRO=patient reported outcomes

2 Background

Registration status

- 2.1 Olaparib with abiraterone received TGA registration on 5 October 2023 for the following indication:
- “Lynparza[®], in combination with abiraterone and either prednisone or prednisolone, is indicated for the treatment of adult patients who have mCRPC with a deleterious or suspected deleterious BRCA mutation (germline or somatic)”.

2.2 Olaparib is also TGA-registered for use as monotherapy for the treatment of mCRPC patients with BRCA1/2 pathogenic variants who have progressed following NHA therapy.

Previous PBAC considerations

2.3 Olaparib monotherapy was recommended by the PBAC in November 2021 for the treatment of mCRPC in patients with BRCA1/2 pathogenic gene variants who have progressed following treatment with a NHA (paragraph 7.1 olaparib Public Summary Document (PSD), November 2021). The PBAC considered that olaparib monotherapy was cost effective at an incremental cost effectiveness ratio (ICER) of \$55,000 to < \$75,000 per quality adjusted life year (QALY) (paragraph 7.9, olaparib PSD, November 2021).

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Olaparib – initial and continuing treatment					
OLAPARIB, Tablet 100mg, 56 Tablet 150mg, 56	\$6,630.78 published price \$ [REDACTED] effective price	2	112	2	LYNPARZA® AstraZeneca
Category / Program: General Schedule (Code GE)					
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>					
Severity: Metastatic					
Condition: Castration resistant metastatic carcinoma of the prostate					
Indication: Castration resistant metastatic carcinoma of the prostate					
Treatment Phase: Initial					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
Clinical criteria:					
The condition must be associated with a class 4 or 5 <i>BRCA1</i> or <i>BRCA2</i> gene mutation, AND The treatment must be/have been initiated within 4 months of treatment initiation of an NHA AND The treatment must be in combination with abiraterone, unless an intolerance to abiraterone requires a temporary or permanent discontinuation of abiraterone AND The treatment must not be used in combination with chemotherapy AND Patient must have a WHO performance status of 2 or less AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug					
Treatment Criteria					
Patient must be undergoing treatment with this drug class for the first time; OR Patient must be undergoing treatment with this drug class on a subsequent occasion, but only because there was an intolerance/contraindication to another drug in the same class that required permanent treatment withdrawal.					

Treatment Phase: Continuing
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not have developed disease progression while receiving treatment with this drug for this condition AND The treatment must be in combination with PBS-subsidised abiraterone for this condition, unless an intolerance to abiraterone requires a temporary or permanent discontinuation of abiraterone
Treatment Criteria
None
Administrative Advice: Special Pricing Arrangements apply

Source: Tables 1.17, 1.18; pp41-42 of the submission.

- 3.1 To allow for delays in BRCA1/2 testing, the sponsor proposed a clinical criterion that allows olaparib to be initiated within four months of initiating an NHA for the treatment of mCRPC. This strategy was not consistent with olaparib’s Product Information, nor the clinical evidence from the PROpel trial, but ESC considered that it was a pragmatic approach to allow for BRCA1/2 testing. The ESC noted that, at present, the current restrictions would not allow a patient who had commenced with enzalutamide to switch to abiraterone (in combination with olaparib) once BRCA1/2 status was confirmed.
- 3.2 The submission proposed an effective dispensed price for maximum quantity (DPMQ) of \$| for olaparib (effective approved ex-manufacturer price (AEMP) = \$| for 56 tablets and \$| for 112 tablets). The requested effective DPMQ was approximately |% higher than the effective DPMQ for olaparib monotherapy in second line mCRPC of \$|. The pre-PBAC response, proposed a reduced AEMP of \$| for 112 tablets which was the same as the existing price for olaparib monotherapy.

For more detail on PBAC’s view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Olaparib is a poly(adenosine diphosphate)-ribose polymerase (PARP) inhibitor. PARP enzymes are involved in DNA transcription, cell cycle regulation and DNA repair, and the anti-tumour effect of PARP inhibitors is dependent on an underlying defect in a cancer cell’s DNA damage response mechanisms.
- 4.2 The proposed clinical algorithm positioned olaparib in combination with abiraterone as an alternative first-line treatment option for mCRPC patients BRCA1/2 pathogenetic variants who are NHA-naïve. The submission did not provide any clinical evidence comparing the proposed place as first-line treatment versus the current algorithm where olaparib monotherapy is provided to BRCA1/2 variant positive patients following treatment with a NHA. Further, the ESC noted that the clinical algorithm in Australia has changed since the PROpel trial was conducted, with the availability of

NHAs earlier in the algorithm for metastatic hormone sensitive prostate cancer (mHSPC) and non-metastatic castration resistant prostate cancer (mOCRPC).

- 4.3 MBS items for tumour and germline BRCA1/2 testing to determine eligibility for access to olaparib in prostate cancer are already established. MBS Items 73303 and 73304 are applicable for determining BRCA status for the proposed population without further amendment. The recommended dose is 300 mg (2×150 mg tablets) twice daily, for a total of 600 mg/day, until progression. Olaparib 100 mg is available if dose reductions are required to manage adverse events (AEs).
- 4.4 The submission explained that patients treated with olaparib would not be eligible to receive another PARP inhibitor following progression on olaparib plus abiraterone treatment. Therefore, the use of the olaparib combination in first line mCRPC would result in fewer patients receiving olaparib monotherapy.
- 4.5 Following recent PBS listings of NHAs for mHSPC and mOCRPC, and the amendment to allow use of enzalutamide and abiraterone prior to docetaxel (paragraphs 5.1 and 5.2, abiraterone enzalutamide PSD, March 2021), the ESC considered that the use of olaparib plus abiraterone is likely to be limited as most patients will have received an NHA prior to reaching the mCRPC stage. The ESC considered that most patients with BRCA1/2 pathogenic variants would continue to receive olaparib monotherapy.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated NHA monotherapy with either enzalutamide or abiraterone as the main comparator. The ESC considered that this was appropriate.
- 5.2 Olaparib monotherapy was not considered a relevant comparator by the submission due to the different place in the treatment pathway (i.e., second line after NHA failure vs. first line combination olaparib).
- 5.3 The submission did not consider docetaxel to be a relevant comparator as the majority of NHA-naïve mCRPC patients would currently receive an NHA following the removal of the requirement for prior docetaxel in the revised PBS restrictions for abiraterone and enzalutamide (paragraph 3.1, abiraterone acetate and enzalutamide PSD, March 2021). Although reasonable, the use of docetaxel in the mCRPC setting may increase as more patients initiate NHAs earlier in the disease pathway.
- 5.4 The submission identified two near-market comparators: the PARP inhibitors niraparib and talazoparib, administered in combination with abiraterone and enzalutamide, respectively. Neither of these agents were TGA-approved in mCRPC.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (10), health care professionals (2) and organisations (17) via the Consumer Comments facility on the PBS website. The comments from individuals and health professionals supported the olaparib submission and noted the benefits including improved survival and quality of life. The comments also not the prohibitive cost of treatment if not subsidised.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the olaparib submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the PROpel trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for olaparib, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison with placebo.
- 6.4 The PBAC also noted input from 16 consumer group organisations (Prostate Cancer Foundation of Australia, Pink Hope, Nepean/Blue Mountains Prostate Cancer Support Group Inc, PROST! Exercise for Prostate Cancer, Bega Valley Prostate Cancer Support Group, South Eastern Prostate Cancer Support Group, Prostate Cancer Support Group Port Macquarie, Grafton Ngerrie (Aboriginal) Mens Cancer Support Group, Bayside Kingston Prostate Cancer Support Group, Prostate Cancer Support Group – ACT and Region, Bairnsdale Prostate Cancer Support Group, Lakes Entrance Prostate Cancer Support Group, Grafton Prostate Cancer Support Group, Parkes Prostate Cancer Awareness and Support Group and Men’s Health and Cancer Support Group of Milton and Ulladulla NSW). These groups noted the improved progression free and survival in patients with BRCA1/2 pathogenic variants treated with olaparib, the benefits to quality of life and described the manageable side effect profile of olaparib. Further, the groups noted the prohibitive cost of olaparib.

Clinical trials

- 6.5 The submission was based on one head-to-head trial comparing olaparib plus abiraterone to placebo to abiraterone, PROpel (N=796).
- 6.6 The PROpel trial recruited genetically unselected mCRPC patients who were stratified by site of distant metastases (bone only vs visceral vs other) and of prior taxane use, but not BRCA status.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

6.7 The clinical claim of superior effectiveness and inferior safety was based on a *post-hoc* subgroup analysis of patients with BRCA1/2 pathogenic variants (n=85). The submission acknowledged that the *post-hoc* analyses had important limitations, including lack of alpha control and lack of stratification by BRCA status.

6.8 Details of the trial presented in the submission are provided in Table 2.

Table 2: Key trial and main reports presented in the submission

Trial ID	Reports
PROpel NCT03732820	DCO1 CSR: Interim analysis – data cut 30 July 2021
	DCO2 CSR: Interim analysis – data cut 14 March 2022
	DCO3 CSR: Final OS Analysis – data cut 12 October 2022
	ODAC [^] Briefing paper 28 th April 2023
	ODAC [^] Presentation 28 th April 2023
	Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Ye D, Mateo J, et al. PROPEL: a randomized, phase III trial evaluating the efficacy and safety of olaparib combined with abiraterone as first-line therapy in patients with metastatic castration-resistant prostate cancer (mCRPC). <i>Journal of clinical oncology</i> . 2019;37:2019-05.

Source: Table 2.4, pp56-57 of the submission.

DCO=data cut-off; ODAC=Oncologic Drugs Advisory Committee

[^] ODAC is a Food and Drug Administration (FDA) advisory committee

6.9 The key features of the PROpel trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Olaparib plus abiraterone vs. abiraterone						
PROpel ITT	796	R, DB, P3, MC ongoing	Low	mCRPC	OS, rPFS	Not used
PROpel BRCA1/2 subgroup	85	R, DB, P3, MC ongoing	High	mCRPC and BRCA1/2-positive	OS, rPFS	Used

Source: Table 2-10, p66 and Table 2.25, p97 of the submission.

BRCA=breast cancer gene; DB=double blind; ITT=intention to treat; MC=multi-centre; mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival; P3=phase 3; R=randomised; rPFS=radiologic progression-free survival.

6.10 The primary outcome was investigator-assessed radiologic progression-free survival (rPFS). The more appropriate blinded independent central review (BICR)-assessed rPFS results were presented for the first data cut-off (DCO) time point (see below).

6.11 The key clinical evidence was sourced from two DCO: 1) DCO1: interim analysis of the rPFS, at a minimum follow-up of 13 months; and 2) DCO3: final analysis of overall survival (OS), 48 months after randomisation. The submission also conducted a final analysis of rPFS (DCO2), after a minimum follow-up of 21 months, but no data were presented for the BRCA1/2 subgroup at this time point.

6.12 Baseline characteristics and disease characteristics were well balanced between treatment groups in the intention to treat (ITT) population, but that was not the case for the BRCA1/2 subgroup.

6.13 Key baseline characteristics were imbalanced in patients with BRCA1/2 pathogenic variants; for example, patients in the abiraterone treatment group were older (71.1% versus 63.8% aged ≥ 65), had a higher proportion of visceral metastases (21.1% versus

10.6%), higher proportion of prior docetaxel treatment (26.3% versus 17.0%), and had worse ECOG performance status (47.4% versus 23.4% with ECOG 1) than patients in the olaparib plus abiraterone combination group. These factors may have biased results against abiraterone monotherapy, particularly given the small number of patients in each treatment group (38 patients treated with abiraterone monotherapy and 47 patients treated with the olaparib plus abiraterone combination).

6.14 The submission identified site of metastases and prior docetaxel treatment as key confounding factors and explained why stratification including these factors was necessary:

- Patients with visceral metastases have been shown to have a shorter survival time compared to patients without visceral metastases from the PREVAIL study, and patients with bone-only metastases have been shown to have longer survival compared to patients with other metastases at baseline from the COU-AA-302 study.
- Docetaxel treatment is only indicated in patients with high disease burden (high volume disease) or with high-risk features at metastatic hormone-sensitive prostate cancer (mHSPC) based on 2 randomized controlled Phase III trials, CHARTED (NCT00309985) and STAMPEDE (NCT00268476). Hence patients with prior docetaxel at mHSPC by default have a poor prognosis compared to patients without prior docetaxel at mHSPC (most likely low disease burden or low-risk patients).”

6.15 The twofold rate of visceral metastases in the abiraterone group was of particular concern. The stratified analysis by metastases site showed a lower rPFS hazard ratio (HR) for the olaparib combination vs. abiraterone in patients with visceral metastases (HR = 0.56; 95% CI: 0.36, 0.87) than in patients with only bone metastases (HR = 0.76; 95% CI: 0.59, 0.98), indicating a greater rPFS benefit for the olaparib combination in patients with visceral metastasis. This was consistent with multivariate analyses conducted in the MAGNITUDE trial of niraparib plus abiraterone (Chi 2023²) which showed the presence of visceral metastases (versus no visceral metastases) significantly increased the risk of progression (HR = 1.608; 95% CI: 1.171, 2.210) and death (HR = 1.694; 95% CI: 1.110, 2.587).

6.16 Overall, these confounding factors and the small sample size result in the magnitude of the effect for olaparib plus abiraterone in the BRCA1/2 subgroup being highly uncertain. The Pre-Sub-Committee Response (PSCR) acknowledged that the PROpel trial was not designed to stratify by BRCA status but stated that the subgroup analysis of BRCA1/2 patients was appropriate given the strong clinical and non-clinical evidence supporting the biological plausibility of differential treatment results in

² Chi KN, et al. MAGNITUDE Principal Investigators. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. *J Clin Oncol.* 2023 Jun 20;41(18):3339-3351.

BRCA1/2 patients. Further, the PSCR presented the results of a multivariate regression analysis that adjusted for potential confounders (including visceral metastases, prior docetaxel treatment, ECOG performance status, age, region, race, PSA and BRCA1/2 mutation) which, compared to the unadjusted results, showed negligible changes in rPFS and OS. The ESC considered that given the small sample size in the BRCA1/2 subgroup, the validity of the regression model adjusted for the number of variables listed above was unclear and that the effects of confounding remained uncertain.

- 6.17 The submission did not present the flow of participants in the BRCA1/2 subgroup, so it was not possible to evaluate the loss to follow up and treatment discontinuation in these patients. This was not appropriate, as the submission requested listing for the BRCA1/2 subgroup only.
- 6.18 The submission also presented a summary of two randomised controlled trials comparing the nominated near-market comparators (talazoparib and niraparib) in combination with NHAs to NHA monotherapy:
- TALAPRO-2 (Agarwal 2023 ³): talazoparib + enzalutamide vs enzalutamide + placebo; and
 - MAGNITUDE (Chi 2023): niraparib + abiraterone vs abiraterone + placebo.

Comparative effectiveness

- 6.19 Table 4 summarises key time to event outcomes from PROpel in the ITT, BRCA1/2-positive and BRCA wild type (WT) populations.

Table 4: Summary of rPFS and OS reported in PROpel

	Number of events/total number of patients (%)		HR (95% CI)	Median duration (95% CI), months	
	OLA+ABI	ABI	HR	OLA+ABI	ABI
rPFS – BICR assessed (DCO1: 30 July 2021)					
ITT	157/399 (39.3)	218/397 (54.9)	0.61 (0.49, 0.74)	27.6 (19.58, NE)	16.4 (13.77, 19.12)
BRCA1/2	12/47 (25.5)	31/38 (81.6)	0.18 (0.09, 0.34)	NE	8.38 (NR, NR)
BRCAwt	141/343 (41.1)	183/350 (52.3)	0.72 (0.58, 0.90)	27.60 (NR, NR)	16.62 (NR, NR)
rPFS – investigator assessed (DCO1: 30 July 2021)					
ITT	168/399 (42.1)	226/397 (56.9)	0.66 (0.54, 0.81)	24.8 (20.47, 27.63)	16.6 (13.93, 19.22)
BRCA1/2	14/47 (29.8)	28/38 (73.7)	0.23 (0.12, 0.43)	NE	8.38 (NR, NR)
BRCAwt	148/343 (43.1)	194/350 (55.4)	0.76 (0.61, 0.94)	27.60 (NR, NR)	16.62 (NR, NR)
rPFS – investigator assessed (DCO3: 12 October 2022) – presented in PSCR					
BRCA1/2	18/47 (38.3)	31/38 (81.6)	0.23 (0.12, 0.40)	38.5 (23.66, NR)	8.38 (5.52, 14.75)
OS (DCO3: 12 October 2022)					
ITT	176/343 (44.1)	205/397 (51.6)	0.81 (0.67, 1.00)	42.05 (38.41, NE)	34.69 (30.95, 39.29)
BRCA1/2	13/47 (27.7)	25/38 (65.8)	0.29 (0.14, 0.56)	NE	22.97 (NR, NR)
BRCAwt	158/343 (46.1)	176/350 (50.3)	0.91 (0.73, 1.13)	39.62 (NR, NR)	37.95 (NR, NR)

Source: Table 2.14, p76; Table 2.26, p98; Table 2.15; Table 27, p99 of the submission; Tables 24-25, DCO1 CSR, and Table ES-1, p5 of the PSCR

Bold = statistically significant

³ Agarwal N, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2023 Jul 22;402(10398):291-303

ABI=abiraterone; BICR=blinded independent central review; BRCA=breast cancer gene; CI=confidence interval; DCO=data cut-off; HR=hazard ratio; ITT=intention to treat; NE=not estimable; NR=not reported; OLA=Olaparib; OS=overall survival; rPFS=radiological progression-free survival; wt=wild type.

6.20 The median duration of follow-up in the ITT population (censored patients) at DCO1 was 19.32 and 19.35 months for the olaparib combination and placebo group, respectively. At DCO3, the corresponding duration of follow up was 32.54 and 44.32 months. These data were not presented for the BRCA1/2 subgroup.

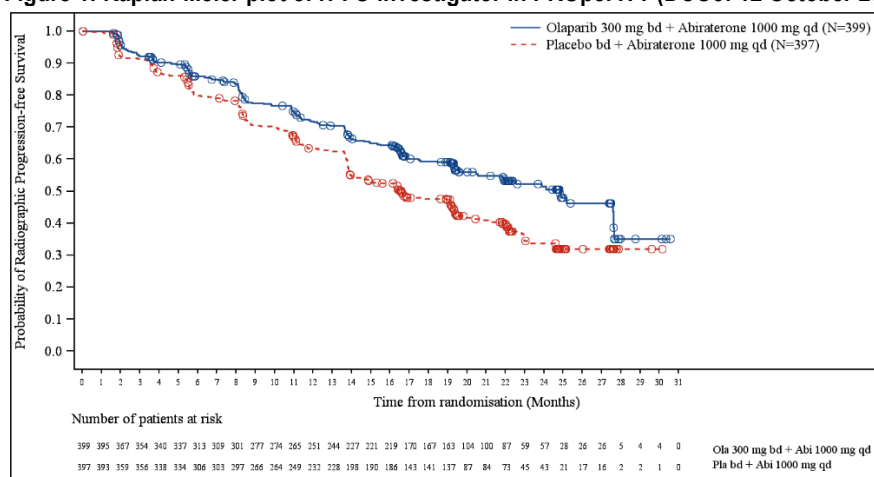
6.21 For the primary outcome of investigator-assessed rPFS at DCO1:

- In the ITT population, there was a statistically significant benefit for olaparib plus abiraterone compared to abiraterone plus placebo (HR = 0.66; 95% CI: 0.54, 0.81), which was maintained through the other data cut-offs.
- In the BRCA1/2 subgroup, the magnitude of the effect of the olaparib plus abiraterone versus abiraterone plus placebo was greater than in the ITT population (HR = 0.23; 95% CI: 0.12, 0.43). As presented in the PSCR, the hazard ratio for rPFS remained consistent at DCO3, and the median rPFS was 38.5 months as compared to 8.38 months for abiraterone plus placebo.

6.22 The small sample size in the BRCA1/2 subgroup highlights the potential lack of power to detect robust differences in rPFS and increases the chance of spurious results between the treatment groups. The first DCO was planned to occur when approximately 379 progression or death events had accrued in 796 patients (47.6% of patients had an event [maturity], information fraction 83.7%), and would provide 94.1% power to show a statistically significant difference in rPFS.

6.23 Figure 1, Figure 2, and Figure 3 present the Kaplan-Meier plots of rPFS in the ITT and BRCA1/2 subgroup.

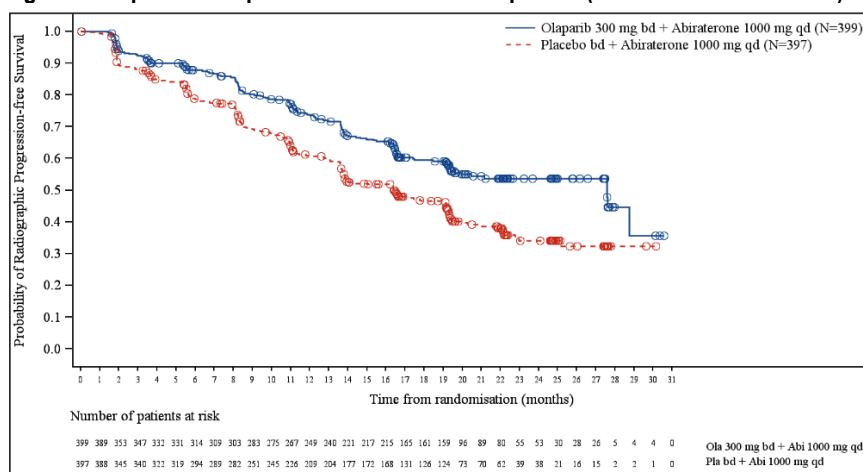
Figure 1: Kaplan-Meier plot of rPFS-investigator in PROpel ITT (DCO3: 12 October 2022)



Source: Figure 2.6, p77 of the submission.

ITT=intention to treat; rPFS=radiological progression-free survival

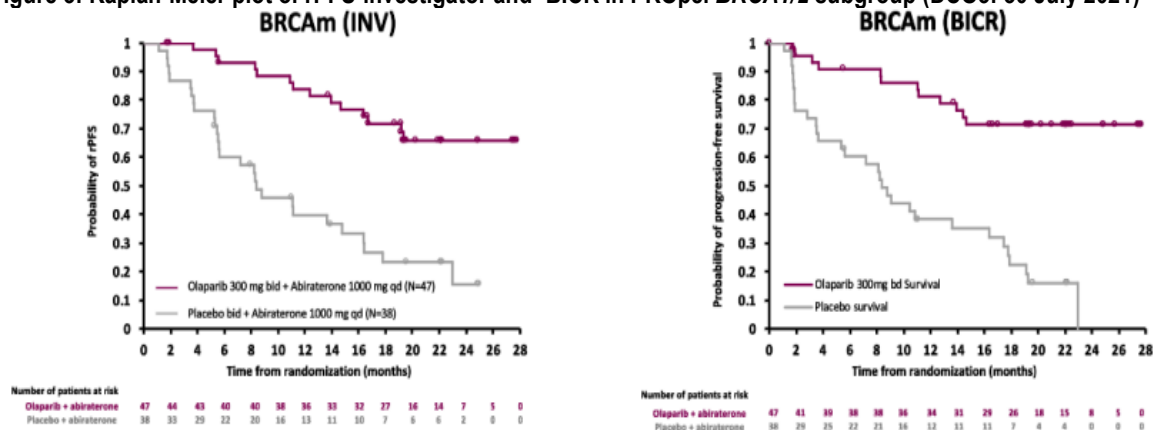
Figure 2: Kaplan-Meier plot of rPFS-BICR in PROpel ITT (DCO3: 12 October 2022)



Source: Figure 4, p101 DCO1 CSR.

BICR= blinded independent central review; ITT=intention to treat; rPFS=radiological progression-free survival

Figure 3: Kaplan-Meier plot of rPFS-investigator and -BICR in PROpel BRCA1/2 subgroup (DCO3: 30 July 2021)



Source: Figure 2.8, p98 of the submission

BICR= blinded independent central review; BRCAm=Breast cancer gene mutation (pathogenic variant); blinded independent central review; INV=investigator; rPFS=radiological progression-free survival

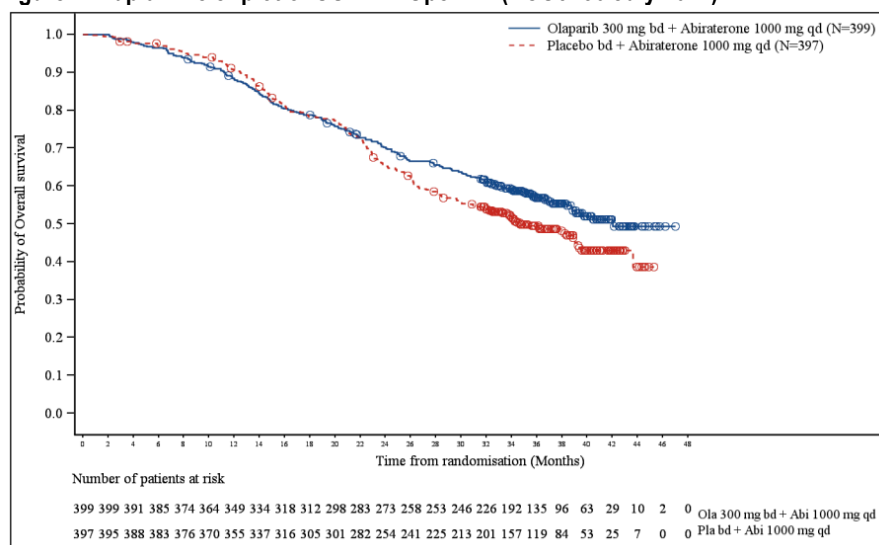
6.24 At the final OS analysis at DCO3, OS data were 47.9% mature (381 events/796 patients) in the ITT. The HR suggested a trend towards improved OS for the olaparib plus abiraterone arm compared to abiraterone plus placebo but did not reach statistical significance (HR = 0.81; 95% CI: 0.67, 1.00).

6.25 In the BRCA1/2 subgroup, patients treated with olaparib plus abiraterone had an improved OS compared to those treated with abiraterone plus placebo (HR = 0.29; 95% CI: 0.14, 0.56). There were only 38 events in the 85 patients in the BRCA1/2 subgroup. These data were immature, and with such small sample size the subgroup analysis lacked power to detect robust differences, increasing the chance of spurious findings. Additionally, as the BRCA1/2 subgroup was not pre-specified, these results should be interpreted with caution. The PSCR stated that the OS results in the BRCA1/2 subgroup were consistent with those reported for second line olaparib monotherapy in the PROfound study (HR = 0.28; 95% CI: 0.10, 0.79, after adjustment for treatment

switching), and that therefore, the results in the BRCA1/2 subgroup in the PROpel trial were highly unlikely to be spurious findings. The PSCR stated that although the data were immature and median OS was not reached in the olaparib plus abiraterone arm, over 70% of patients remained alive at 3 years, as compared to a median survival of 23.6 months in the abiraterone plus placebo arm. The PSCR also stated that no longer term data are expected from the PROpel trial and that no further trials for olaparib and abiraterone in mCRPC are planned.

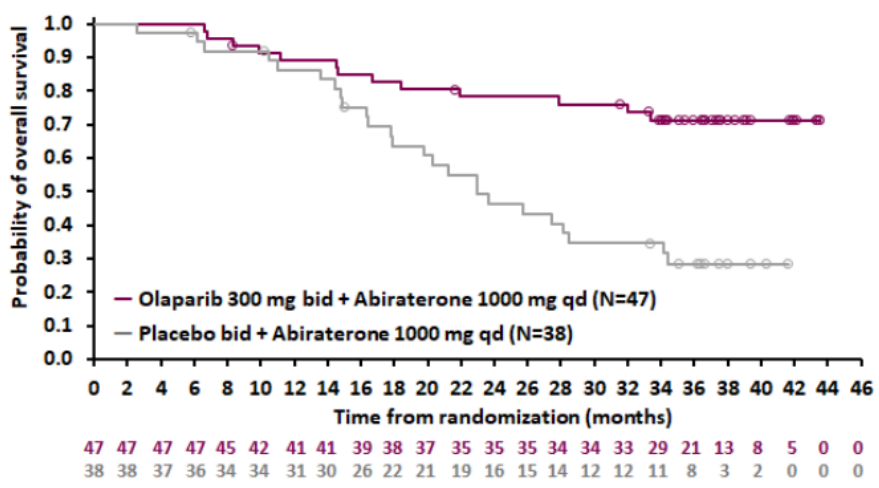
6.26 Figure 4 and Figure 5 present the Kaplan-Meier plots of OS in the ITT and BRCA1/2 subgroup.

Figure 4: Kaplan-Meier plot of OS in PROpel ITT (DCO3: 30 July 2021)



Source: Figure 2.7 of the submission
Bd=twice daily; DCO=data cut off; qd=once daily; ITT=intention to treat, OS=overall survival.

Figure 5: Kaplan-Meier plot of OS in PROpel BRCA1/2 subgroup (DCO3: 30 July 2021)



Source: Figure 2.9, p99 of the submission
Bd=twice daily; BRCA=breast cancer gene; DCO=data cut off; qd=once daily; OS=overall survival.

6.27 Other secondary outcomes presented in the submission are summarised in Table 5.

Table 5: Secondary outcomes in PROpel (DCO3: 12 October 2022)

	Number of events/total number of patients (%)		HR (95% CI)	Median duration (95% CI), months	
	OLA+ABI	ABI	HR	OLA+ABI	ABI
Time to first subsequent therapy or death (TFST)					
ITT	225 (63.9)	285 (71.8)	0.76 (0.64, 0.90)	24.6 (21.1, 28.5)	19.4 (17.0, 21.1)
BRCA1/2	24 (51.1)	30 (78.9)	0.35 (0.21, 0.61)	37.39	14.75
BRCAwt	224 (65.3)	250 (71.4)	0.84 (0.70, 1.01)	23.95	19.91
Time from randomisation to second progression or death (PFS2)					
ITT	103 (25.8)	126 (31.7)	0.76 (0.59, 0.99)	NE	NE
BRCA1/2	9 (19.1)	15 (39.5)	0.31 (0.13, 0.69)	NE	22.97
BRCAwt	92 (26.8)	108 (30.9)	0.86 (0.65, 1.14)	NE	NE
Time to first symptomatic skeletal-related event (SSRE)					
ITT	46 (11.5)	51 (12.8)	0.82 (0.55, 1.22)	NE	NE
BRCA1/2	NR	NR	NR	NR	NR
BRCAwt	NR	NR	NR	NR	NR

Source: Table 2.16, p79; Tables 2.28-2.29, p100;

ABI=abiraterone; BRCA=breast cancer gene; CI=confidence interval; DCO=data cut-off; HR=hazard ratio; ITT=intention to treat;

OLA=Olaparib; NE=not estimable; NR=not reported

6.28 Time to first symptomatic skeletal-related event (SSRE) was only presented for the ITT population. This was not appropriate, as this outcome was included in the economic model and potential differences in SSREs between the ITT and BRCA1/2 subgroup could not be evaluated.

6.29 The submission did not present EQ-5D-5L for any of the trial populations, even though EQ-5D-5L data for the ITT population were included in the CSR. However, no statistical analyses comparing the two treatment groups were conducted. This was inappropriate, given utility values in the economic model were derived from EQ-5D-5L data in PROpel and the submission assumed the same health state utilities for both treatment groups.

Comparative harms

6.30 Table 6 presents a summary of key AEs in the ITT and BRCA1/2 subgroups of PROpel.

6.31 The submission used safety data from the ITT population to inform the economic model, explaining this was due to the small sample size in the BRCA1/2 subgroup. This was appropriate given the lack of power to detect differences in the BRCA1/2 subgroup, and as many of the key events presented for the ITT population were missing in the BRCA1/2 subgroup, particularly regarding treatment interruptions, dose reductions, and discontinuation due to AEs. These results were provided in the PSCR.

Table 6: Summary of key adverse events in PROpel (DCO3: 12 October 2022)

AE category	ITT			BRCA1/2	
	OLA + ABI n/N (%)	ABI n/N (%)	RD (95%CI)	OLA + ABI n/N (%)	ABI n/N (%)
Any AE	389/398 (97.7)	380/396 (96.0)	0.02 (-0.01, 0.04)	47/47 (100)	34/38 (89.5)
Any AE causally related to olaparib/placebo *	316/398 (79.4)	227/396 (57.3)	0.22 (0.16, 0.28)	NR	NR
Any AE of Grade ≥3	222/398 (55.8)	171/396 (43.2)	0.13 (0.06, 0.19)	23/47 (48.9)	15/38 (39.5)
Any AE leading to death	26/398 (6.5)	20/396 (5.1)	0.01 (-0.02, 0.05)	1/47 (2.1)	2/38 (5.3)
Any SAE	161/398 (40.5)	126/396 (31.8)	0.09 (0.02, 0.15)	14/47 (29.8)	12/38 (31.6)
Any AE leading to discontinuation of study treatment ^a	71/398 (17.8)	43/396 (10.9)	0.07 (0.02, 0.12)	NR	NR
Any AE leading to dose reduction of study treatment ^a	112/398 (28.1)	56/396 (14.1)	0.14 (0.08, 0.20)	ABI: 0 OLA/PBO: 10/47 (21.3)	ABI: 2/38 (5.3) OLA/PBO: 1/38 (2.6)
Any AE leading to dose interruption of study treatment ^a	206/398 (51.8)	128/396 (32.3)	0.19 (0.13, 0.26)	ABI: 16/47 (34.0) OLA/PBO: 26/47 (55.3)	ABI: 10/38 (26.3) OLA/PBO: 10/38 (26.3)
Any AE leading to discontinuation of olaparib/placebo	69/398 (17.3)	34/396 (8.6)	0.09 (0.04, 0.13)	6/47 (12.8)	4/38 (10.5)
Any AE leading to discontinuation of abiraterone	45/398 (11.3)	37/396 (9.3)	0.02 (-0.02, 0.06)	3/47 (6.4)	4/38 (10.5)

Bold =statistically significant difference

Source: Table 2.19, p82; Table 2.31, p102 of the submission, and Table ES-2, p5 of the PSCR.

ABI=abiraterone; AE=adverse event; BRCA=breast cancer gene; CI=confidence interval; n=number of participants reporting events; N=total participants in group; NR=not reported; OLA=Olaparib; PBO = placebo; RD=risk difference; SAE=serious adverse event

^a Study treatment^a refers to olaparib/placebo, and/or abiraterone, and/or prednisone/prednisolone.

^b Patients with multiple events in the same category are counted only once in that category. Patients with events in > 1 category are counted in each of those categories.

- 6.32 Overall, safety results in the ITT population showed that olaparib plus abiraterone has a worse safety profile compared to abiraterone monotherapy. In particular, patients treated with olaparib plus abiraterone experienced significantly higher number of serious AEs and grade ≥3 AEs than patients in the abiraterone monotherapy arm. Patients in the olaparib plus abiraterone group also had significantly more AEs leading to treatment discontinuation, interruption, and dose reductions.
- 6.33 In the BRCA1/2 subgroup, the numbers of events in both treatment arms were too small to confidently establish any differences in safety between treatments; the confidence intervals around the risk differences for all outcomes were large and crossed zero (therefore, not presented in the table above).
- 6.34 The submission identified venous thromboembolism (VTE) as an adverse drug reaction associated with olaparib in PROpel. A cumulative review of VTE and pulmonary embolism was performed by the sponsor using all available sources including non-clinical, clinical, post-marketing data and literature and concluded that there was

sufficient evidence to suggest a causal relationship between olaparib and VTE/pulmonary embolism. The TGA delegate recommended (TGA delegate overview) Product Information revision discussions will need to include consideration of this issue, and “The Warnings and Precautions” section will require revision for consistency and clinical utility.

Benefits/harms

6.35 A summary of the comparative benefits and harms for olaparib plus abiraterone versus abiraterone monotherapy is presented in Table 7.

Table 7: Summary of comparative benefits and harms for olaparib plus abiraterone and abiraterone

Benefits – PROpel BRCA1/2 subgroup						
	OLA + ABI N=47	ABI N=38	Absolute difference	HR (95% CI)		
rPFS DCO1^a (BICR-assessed)						
Event n/N (%)	12/47 (25.5)	31/38 (81.6)	-	0.18 (0.09, 0.34)		
% progression-free (95% CI)	NR	NR	-			
Median months to rPFS (95% CI)	NE	8.38 (NR, NR)	-			
rPFS DCO1^a (investigator-assessed)						
Event n/N (%)	14/47 (29.8)	28/38 (73.7)	-	0.23 (0.12, 0.43)		
% progression-free (95% CI)	NR	NR	-			
Median months to rPFS (95% CI)	NE	8.38 (NR, NR)	-			
OS DCO3^a						
Died n (%)	13/47 (27.7)	25/38 (65.8)	-	0.29 (0.14, 0.56)		
% alive (95% CI)	NR	NR	-			
Median months to death (95% CI)	NE	22.97 (NR, NR)	-			
Harms – PROpel ITT						
AE Grade≥3	OLA + ABI N=398	ABI N=396	RR (95% CI)	Events/100 patients		RD (95% CI)
				OLA + ABI	ABI	
Any Grade≥3	389/398	380/396	1.29 (1.12, 1.49)	98	96	0.13 (0.06, 0.19)
Anaemia	64/398	13/396	4.90 (2.74, 8.75)	16	3	0.13 (0.09, 0.17)
PE	29/398	9/396	3.21 (1.54, 6.68)	7	2	0.05 (0.02, 0.08)

BOLD=statistically significant.

Source: compiled during the evaluation

ABI=abiraterone; BRCA=breast cancer gene, BICR=blinded independent central review; CI=confidence interval; DCO=data cut-off; HR=hazard ratio; OLA=olaparib; PE=pulmonary embolism; RD=risk difference; RR=risk ratio

^a Duration of follow-up: DCO1=minimum 13 months; DCO3: expected 48 months.

* {Median/Maximum} duration of follow-up: Trial I = 7.5 months; Trial II = 8 months; Trial III = 8.5 months; Trial IV = 12 months; Trial V = 13.5 months; Trial VI = 12.5 months, etc

6.36 As no rPFS or OS data were presented at specific time points for the BRCA1/2 subgroup, no statements regarding the number of patients progression-free or number of patients alive when treated with olaparib plus abiraterone compared to abiraterone monotherapy can be made. In regard to harms, safety data in the BRCA1/2 subgroup were unreliable and only ITT safety results were applied to the economic model.

6.37 On the basis of the direct evidence presented by the submission for the ITT population, for every 100 patients treated with olaparib plus abiraterone in comparison with abiraterone monotherapy:

- Approximately 13 more additional patients would experience grade ≥ 3 anaemia, 5 additional patients would experience grade ≥ 3 pulmonary embolism, and approximately 2 patients will experience an additional grade ≥ 3 AE.

Summary of other trials of PARP inhibitor in combination

- 6.38 Key results for the genetically unselected/ITT population and the BRCA1/2 subgroups across PROpel, TALAPRO-2 and MAGNITUDE are presented in Table 8.
- 6.39 MAGNITUDE was the only trial that stratified patients by BRCA status and had enough power to detect rPFS differences between treatment arms. TALAPRO 2 conducted a *post-hoc* subgroup analysis of rPFS by BRCA status using an unstratified Cox model with treatment as the only covariate due to the small number of patients. As with PROpel, both TALAPRO-2 and MAGNITUDE are still ongoing.

Table 8: Key results for the genetically unselected/ITT population and the BRCA1/2 subgroup in PROpel, TALAPRO-2, and MAGNITUDE.

Trial	PROpel		TALAPRO-2		MAGNITUDE	
	OLA+ABI	PBO+ABI	TALA+ENZA	PBO+ENZA	NIRA+ABI	PBO+ABI
Genetically unselected/ITT populations						
rPFS BICR						
Events n/N (%)	182/399 (45.6)	242 /397(61.0)	151/402 (38)	191/403 (47)	NR	NR
Median rPFS, months	27.6	16.5	NR	21.9	NR	NR
HR (95% CI)	0.62 (0.51, 0.75)		0.63 (0.51, 0.78)		NR	
rPFS investigator						
Events, n/N (%)	219/399 (55)	277/397 (70)	119/402 (29.6)	153/403 (38.0)	NR	NR
Median rPFS, months	25.0	16.5	NR	30.3	NR	NR
HR (95% CI)	0.68 (0.57, 0.81)		0.64 (0.50, 0.81)		NR	
OS						
Events, n (%)	176/399 (44.1)	205/397 (51.6)	123/402 (30.6)	129/403 (32.0)	NR	NR
Median OS, months	42.1	34.7	36.4	NR	NR	NR
HR (95% CI)	0.81 (0.67, 1.00)		0.89 (0.69,1.14)		NR	
BRCA1/2 subgroups						
rPFS BICR						
Events, n/N (%)	12/47 (25.5)	31/38 (81.6)	8/27 (29.6)	22/32 (68.7)	NE	NE
Median rPFS, months	NE	8.4	NR	NR	16.6	10.9
HR (95% CI)	0.18 (0.09,0.34)		0.23 (0.10, 0.53)		0.53 (0.36,0.79)	
rPFS investigator						
Events, n/N (%)	14 (29.8)	28 (73.7)	NR	NR	NE	NE
Median rPFS, months	NE	8.4	NR	NR	19.3	12.4
HR (95% CI)	0.23 (0.12, 0.43)		NR		0.50 (0.33, 0.75)	
OS						
Events, n (%)	13 (27.7)	25 (65.8)	NE	NE	27/113 (23.9)	29/112 (25.9)
Median OS, months	NE	22.97	NE	NE	NE	NE
HR (95% CI)	0.29 (0.14, 0.56)		NR		0.96 (0.57,1.63)	

Bold =statistically significant results

Source: Tables 9 and 11, ITC Appendix A. TALAPRO-2 publication.

ABI=Abiraterone; BRCA=breast cancer gene, BICR=blinded independent central review; ENZA=enzalutamide; HR=hazard ratio; HRR=homologous recombination repair gene; KM=Kaplan Meier; NA, not applicable; NE=not-estimable; NR=not reported; OLA=olaparib; PBO=placebo; rPFS=radiological progression-free survival; TALA=talazoparib

- 6.40 Across the trials, rPFS was significantly improved in patients treated with PARP inhibitors plus NHA compared to NHA monotherapy, but the magnitude of the effect

differed. HRs for progression in the ITT and BRCA1/2 subgroups were similar in the PROpel and TALAPRO-2 trials, whereas the HR in the BRCA1/2 subgroup in MAGNITUDE was much higher (i.e., smaller magnitude of effect for PARP inhibitor plus NHA versus NHA monotherapy). The difference in OS HRs in the BRCA1/2 subgroups was also considerable between PROpel and MAGNITUDE, but neither of these trials had mature OS data and there was a very high level of uncertainty around the OS estimates.

- 6.41 A plausible explanation for these variations could be the lack of stratification by BRCA status and statistical power in PROpel and TALAPRO-2, which could have biased results. There were other differences between the trials that also need to be considered, such as the different NHA combinations (enzalutamide vs. abiraterone) and possible differences in the baseline characteristics of BRCA1/2 patients (not reported in TALAPRO-2 and MAGNITUDE). It is also possible that efficacy/potency of various PARP inhibitor combinations may differ.
- 6.42 In terms of safety outcomes, PARP inhibitors in combination with NHA had a worse safety profile compared to NHA monotherapy, driven by significantly higher grade ≥ 3 AEs. There were no safety data presented for patients with BRCA1/2 pathogenic variants.
- 6.43 A systematic review and meta-analysis of these PARP inhibitor trials (including PROpel) by Sayyid et al. 2023⁴ noted that first-line addition of PARP inhibitors was associated with a 45% relative risk increase in grade ≥ 3 TEAEs, including a 6.22-fold increase for grade ≥ 3 anaemia (31.9% versus 4.9%). The authors stated that this significantly worse toxicity profile raised concerns as to whether routine first-line addition of PARP inhibitors for mCRPC patients can be considered standard of care therapy, even in patients with homologous recombination repair gene pathogenic variants, in the absence of a clear OS benefit.

Clinical claim

- 6.44 The submission described olaparib plus abiraterone as superior in terms of effectiveness compared to abiraterone monotherapy. The ESC considered that this claim was supported in the ITT population and was likely, but the magnitude of effect was uncertain, in the BRCA1/2 subgroup as:
- *Post-hoc* subgroup analyses in patients with BRCA1/2 pathogenic variants were highly uncertain given the small patient numbers and imbalanced baseline characteristics between treatment arms, particularly in key confounding factors such as visceral metastases and prior docetaxel treatment.

⁴ Sayyid RK, et al. PARP Inhibitor Combinations in First Line mCRPC: A Systematic Review and Meta-Analysis. BJU Int. 2023 Jul 17. Online ahead of print.

- Key data were missing for the BRCA1/2 subgroup such as the flow of participants and treatment exposure.
- OS data were immature.
- Evidence from other trials of PARP inhibitors in combination with NHAs indicated a likely rPFS benefit for the combination treatment, but OS data were immature and, so far, there was no significant benefit over NHA monotherapy. The only PARP inhibitor trial that stratified the analysis by BRCA1/2 status reported a considerably lower magnitude of effect compared to PROpel for rPFS, and a HR for OS close to 1 (which was not statistically significant).

6.45 The PBAC considered that the claim of superior comparative effectiveness in the BRCA1/2 subgroup was likely reasonable, but the magnitude of effect was highly uncertain. Furthermore, the PBAC considered that the comparative effectiveness of olaparib plus abiraterone was uncertain compared to olaparib monotherapy based on the data available.

6.46 The submission described olaparib plus abiraterone as inferior in terms of safety compared to abiraterone monotherapy. The ESC considered that this claim was adequately supported in the ITT population and the BRCA1/2 subgroup.

6.47 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.48 The submission presented a stepped economic evaluation based on the PROpel trial. The modelled economic evaluation was a cost-utility analysis using a partitioned survival model with three health states: progression free (PF), progressed disease (PD), and death. Table 9 provides a summary of model components.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Olaparib plus abiraterone vs NHA monotherapy
Time horizon	15 years in the model base case vs. 36 months (median follow-up) in the trial. This was reduced to 10 years in the pre-PBAC response.
Outcomes	Progression-free years gained, life-years gained, quality-adjusted life years gained
Methods used to generate results	Partitioned survival model
Health states	Progression-free, progressed, death
Cycle length	Monthly
Transition probabilities or Allocation to health states	Health state allocation was determined by rPFS and OS curves from the BRCA1/2 subgroup in PROpel
Extrapolation method	Parametric models independently fitted to each treatment arm based on statistical (AIC and BIC) and visual fit, as well as clinical plausibility, OS: exponential (intervention) and log-logistic (comparator), PFS: log-normal, ToT: exponential ^a . The pre-PBAC response applied the conservative Weibull distributions for all extrapolations.
Health related quality of life	ITT population of PROpel: PF=0.82, PD=0.78.

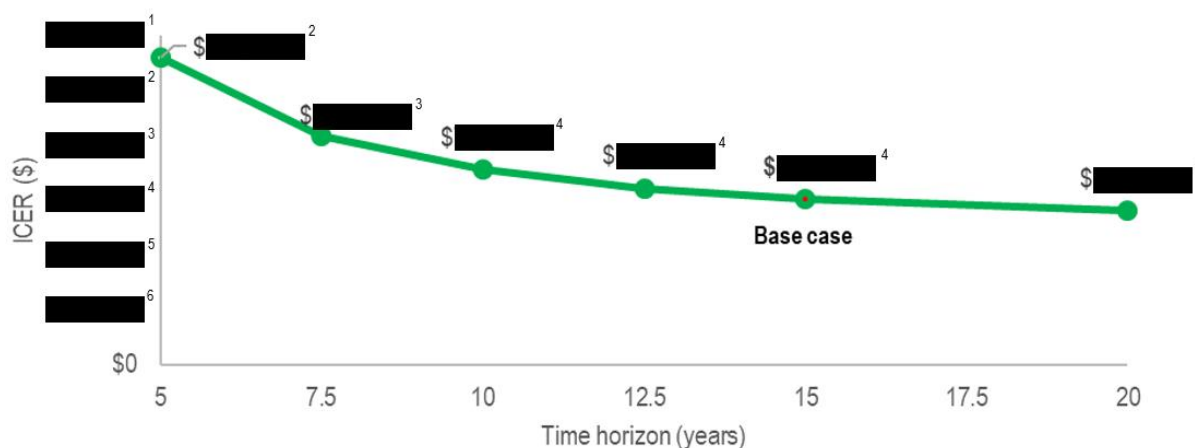
Source: Compiled during the evaluation.

AIC=Akaike information criterion, BIC=Bayesian information criterion, ITT=intention to treat, NHA=novel hormonal agents, OS=overall survival, PD=progressive disease, PF=progression free, rPFS= radiologic progression-free survival, ToT=time on treatment

^a ToT extrapolation was based on visual fit only.

- 6.49 The submission nominated a time horizon of 15 years in the base case (10 and 20 years in sensitivity analyses). The submission argued that 15 years were required to reflect all important differences in cost and outcomes, given 20% of patients in the olaparib plus abiraterone arm and 0.9% of patients in the NHA monotherapy arm were expected to remain alive in the model. A shorter time horizon may be more appropriate given the high uncertainty surrounding OS data in the BRCA1/2 subgroup of PROpel and the poor prognosis of these patients. The PSCR reiterated that the 15-year time horizon was appropriate given the improvements in PFS (median rPFS = 38.5 months compared to 8.4 months in the placebo arm) and OS (70% of patients alive at 3 years) observed in BRCA1/2 patients treated with olaparib plus abiraterone.
- 6.50 Further, a 15-year time horizon was also not consistent with previous PBAC recommendations in advanced prostate cancer. The PBAC had considered a 10-year time horizon appropriate for darolutamide in non-metastatic (m0CRPC (paragraph 5.9, darolutamide PSD, July 2021); and 10-year and 5-year time horizons appropriate for apalutamide in low-volume and high-volume mHSPC, respectively (Table 2, apalutamide PSD, July 2022). Both m0CRPC and mHSPC are earlier stages in the disease pathway compared to first line mCRPC (as requested for olaparib plus abiraterone in this submission). The PBAC previously recommended a time horizon of 5 years for olaparib in second line BRCA-positive mCRPC (paragraph 6.83, olaparib PSD, November 2021). The pre-PBAC response proposed a revised base case in which the time horizon was 10 years, stating that 10 years was sufficient to mitigate the uncertainty associated with the longer extrapolations and would capture the majority of benefits of treatment with olaparib in this setting.
- 6.51 Figure 6 presents how the ICER increases as the time horizon is reduced from 15 years in the base case to 5 years.

Figure 6: ICER changes over modelled time horizon (years)

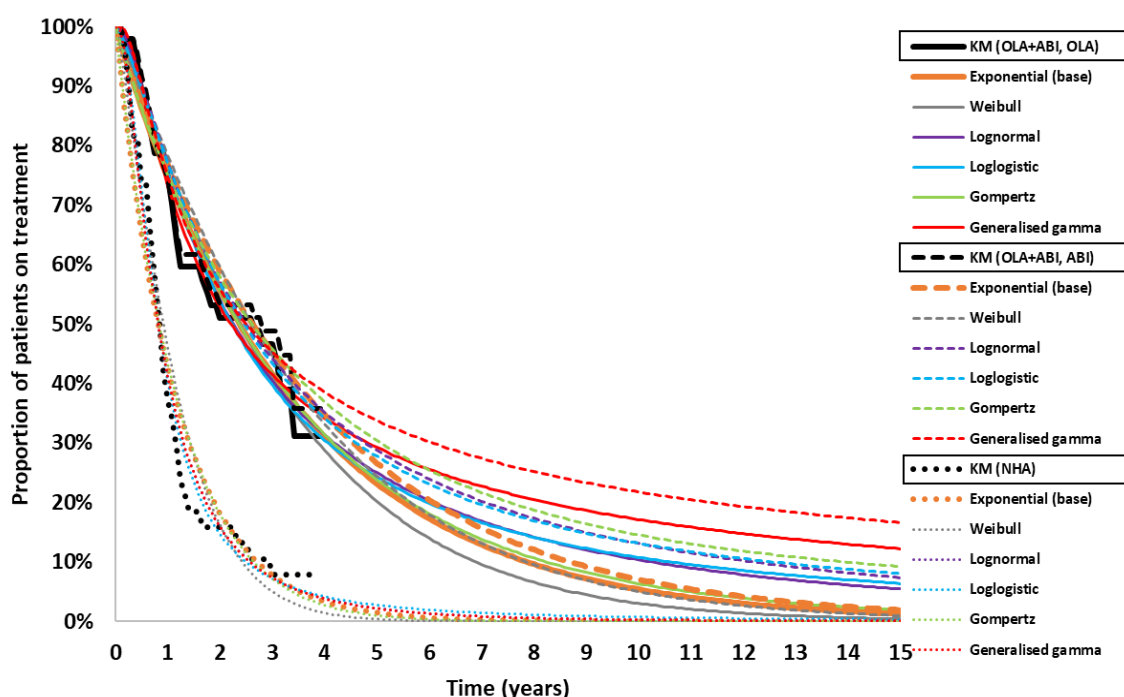


Source: Compiled during the evaluation
 ICER=incremental cost-effectiveness ratio
 The redacted values correspond to the following ranges:
 1 \$115,000 to < \$135,000
 2 \$95,000 to < \$115,000
 3 \$75,000 to < \$95,000
 4 \$55,000 to < \$75,000
 5 \$35,000 to < \$45,000
 6 \$15,000 to < \$25,000

- 6.52 Outcomes in the model were based on PROpel; however, the submission used data from the ITT population and BRCA1/2 subgroup inconsistently throughout the model. Survival inputs (OS and rPFS) were derived from patient-level data in the BRCA1/2 subgroup, while baseline characteristics, utility values, safety data, and subsequent treatments were obtained from the ITT population.
- 6.53 The submission stated that time on treatment (ToT) for olaparib, abiraterone (in combination with olaparib) and NHA monotherapy were extrapolated using the exponential function from patient-level data from the BRCA1/2 subgroup in PROpel. The extrapolation was conducted based on a visual assessment of model curves (Figure 7). The submission did not specify which data were used to derive the ToT Kaplan-Meier curves applied in the model. This created a high level of uncertainty around these estimates, given treatment exposure data for the BRCA1/2 subgroup were not presented by the submission. A sensitivity analysis conducted during the evaluation to explore the impact of using PFS data as proxy for ToT increased the ICER by 1% to \$75,000 to < \$95,000 from a base case of \$55,000 to < \$75,000 per QALY gained. The PSCR presented the duration of exposure data for the BRCA1/2 subgroup which indicated that the median ToT in the PROpel trial was 31.44 months in the olaparib plus abiraterone arm and 9.85 months in the abiraterone plus placebo arm.
- 6.54 Based on the submission's extrapolated ToT Kaplan-Meier curve for the abiraterone monotherapy arm, the mean duration of treatment for NHA monotherapy in the model 14.3 months. This may be an overestimate compared to mean NHA treatment duration on the PBS. A recent DUSC analysis in April 2022 indicated the average PBS treatment durations for abiraterone and enzalutamide were 9 and 12 months,

respectively, or 11.8 months combined (assuming zero treatment breaks). However, the DUSC estimates were not specific to a BRCA1/2 population (paragraph 6.26, apalutamide PSD, July 2022). The PSCR stated that reducing the duration of NHA monotherapy treatment to 11.8 months increased the ICER by 1.1%, indicating that it was not a key driver of the model. The ESC considered that the duration of NHA monotherapy in BRCA1/2 patients was likely to be less than that estimated by DUSC as these patients do not respond as well to NHA therapy.

Figure 7: Extrapolation of ToT for the olaparib plus abiraterone and NHA arms of the model



Source: compiled during the evaluation

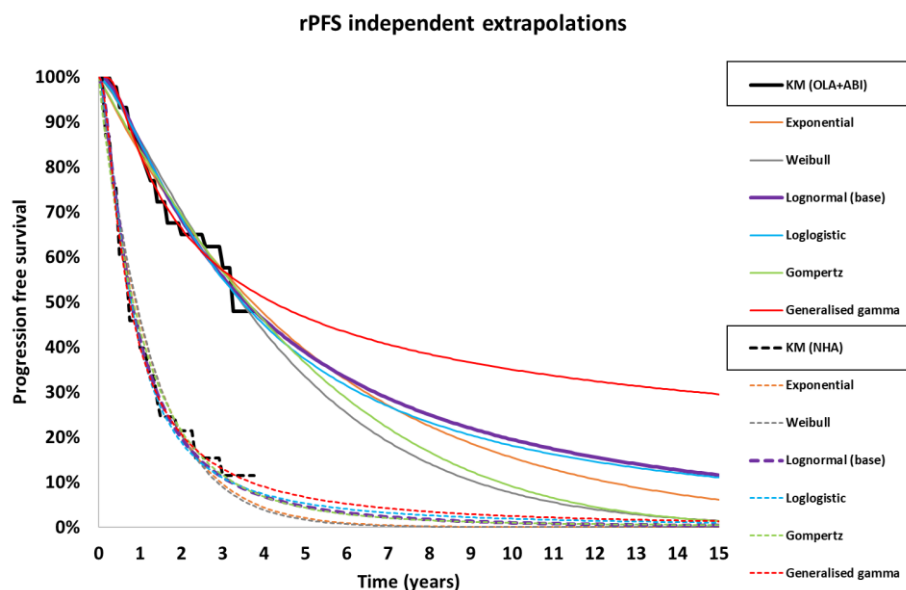
Note: extrapolation truncated to 60 months

ABI=abiraterone, KM=Kaplan-Meier, NHA=new hormonal agents, OLA=olaparib, ToT=time on treatment

6.55 The model extrapolated PFS and OS Kaplan-Meier data in the BRCA1/2 subgroup from median follow-up (36 months) using independently-fitted parametric extrapolations for each treatment arm. The sponsor conducted a sensitivity analysis assuming proportional hazards using the hazard ratios reported in PROpel (OS = 0.29, PFS = 0.23). This resulted in a minimal increase in the ICER (0.81%).

6.56 A log-normal function was selected for the extrapolation of rPFS in both arms (Figure 8).

Figure 8: Extrapolation of rPFS for the olaparib plus abiraterone and NHA arms of the model



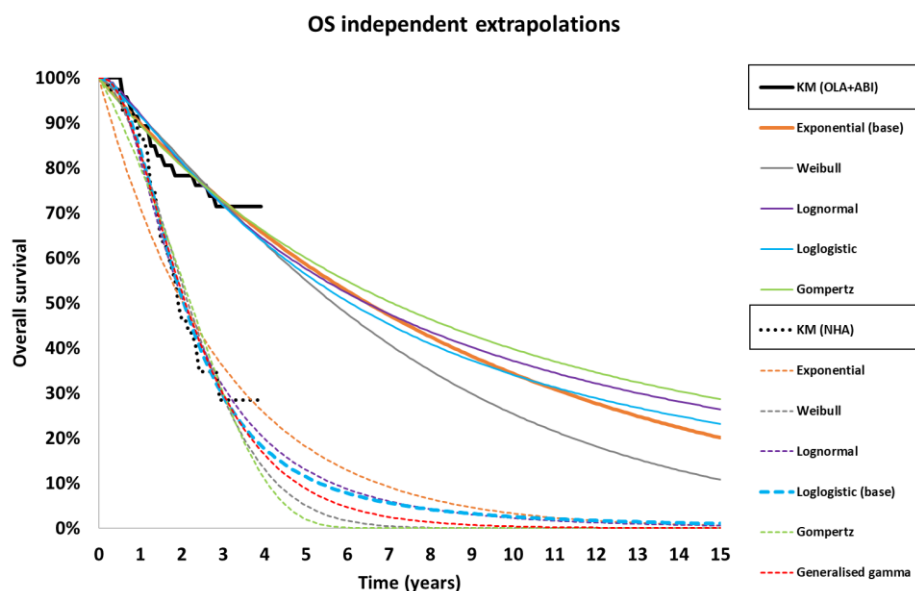
Source: Compiled during the evaluation

Note: extrapolation truncated to 60 months

ABI= abiraterone, KM=Kaplan-Meier, NHA= novel hormonal agent, OLA=olaparib, rPFS= radiological progression free survival

6.57 Exponential and log-logistic were chosen for OS in the intervention and comparator arms, respectively (Figure 9).

Figure 9: Extrapolation of OS for the olaparib plus abiraterone and NHA arms of the model



Source: compiled during the evaluation

Note: extrapolation truncated to 60 months

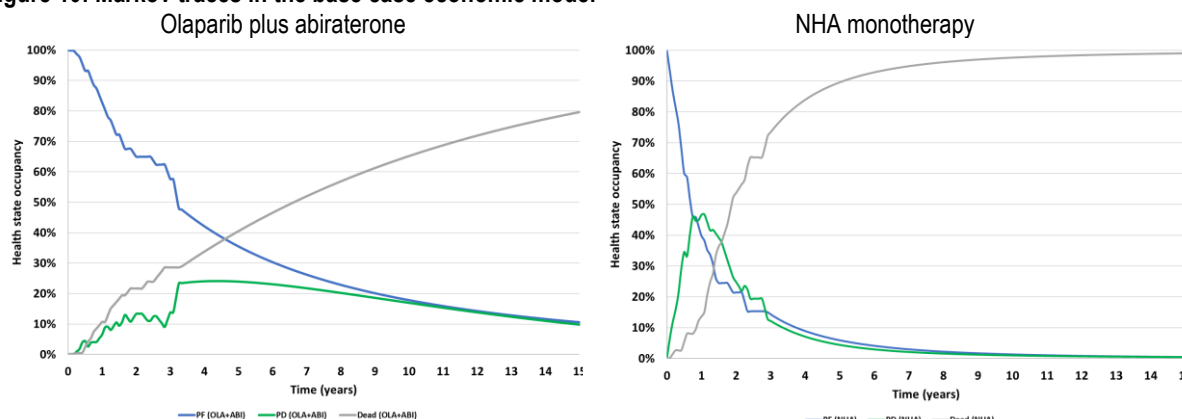
ABI=abiraterone, KM=Kaplan-Meier, NHA= novel hormonal agents, OLA=olaparib, OS=overall survival

6.58 Overall, most extrapolated curves (except gamma for PFS and exponential for OS) showed general good fit for the Kaplan-Meier data and only diverged in the tail section. The effect of using a more conservative distribution in the OS extrapolation,

such as Weibull, was evaluated in the sensitivity analysis and increased the ICER by 8.36% to \$55,000 to < \$75,000 from a base case of \$55,000 to < \$75,000 per QALY gained.

- 6.59 Extrapolations of rPFS and ToT Kaplan-Meier data showed that ToT exceeded the PFS duration in the NHA monotherapy arm for the first 12 months. This suggested that some patients in the NHA arm continued treatment after experiencing disease progression. This does not reflect clinical practice, where patients cease treatment upon disease progression. The PSCR updated the economic model to ensure that ToT could not exceed PFS at any point in both treatment arms but noted that the correction had a minimal impact on the ICER (0.52% increase).
- 6.60 Given the uncertainty around the magnitude of the survival benefit, the estimated survival rate of 20% after 15 years for olaparib plus abiraterone may not be justified. The PSCR reiterated that the statistically best fitting functions were applied to extrapolated OS data beyond the trial period. The ESC considered the clinical plausibility of the partitioned survival model to be uncertain as the modelled OS benefit did not align with clinical evidence of the prognosis of this patient group. Further, the ESC considered that it was not reasonable to assume that the OS difference observed at 36 months in the trial would be sustained over the 15-year time horizon of the model. Given the PBACs prior recommendations, the ESC considered that a time horizon of 7.5 years would be appropriate and that there should be convergence of the OS curves within this time, particularly given the poorer prognosis of patients with BRCA1/2 pathogenic variants.
- 6.61 To further reduce uncertainty, the pre-PBAC response applied the more conservative Weibull distributions to all extrapolations in the revised base case, noting that this reduced the proportion of patients alive in the olaparib arm at 10 years from 35% to 26%, the proportion of patient's progression free from 18% to 7% and the duration of treatment from 41 months to 37 months. The pre-PBAC response stated that converging the OS curves was not appropriate given the OS benefit observed in the trial.
- 6.62 The Markov traces presented in Figure 10 demonstrate that differences between the two treatment arms were primarily derived from the extrapolated variations in OS, with greater numbers of patients alive with olaparib plus abiraterone combination treatment compared to NHA monotherapy. This constitutes the main source of uncertainty in the model.

Figure 10: Markov traces in the base case economic model



Source: Figure 3-9 and 3-10, p146 of the submission and constructed during the evaluation using data presented in “Markov trace” worksheet in the Excel workbook “Attachment 3.1- Cost Effectiveness Model”.

ABI=abiraterone, NHA=novel hormonal agent, OLA=olaparib, PD=progressed disease, PF=progression-free, TOT=time on treatment

6.63 Noting that the ICER was very sensitive to the olaparib plus abiraterone survival benefit, the evaluators provided a sensitivity analysis which assumed a similar survival benefit across PARP inhibitors and adjusted the Kaplan-Meier curves based on benefits observed in the MAGNITUDE trial (stratified by BRCA1/2 status), with a significant difference in PFS (HR = 0.53; 95% CI: 0.36, 0.79) but not in OS (HR = 0.96; 95% CI: 0.57, 1.63). This increased the ICER to > \$1,055,000 per QALY gained from a base case of \$55,000 to < \$75,000. The PSCR stated that applying the hazard ratios from the MAGNITUDE trial was not appropriate as there were important differences between olaparib and niraparib including that olaparib inhibits PARP1/2/3 whereas niraparib inhibits PARP1/2. Further the PSCR stated that in the MAGNITUDE trial, (i) patients received reduced doses of niraparib (200 mg rather than 300 mg per day), and (ii) significantly more patients in the placebo arm received PARP inhibitor therapy post progression. The ESC noted that the FDA label recommends a dosage of 200 mg per day for niraparib in the BRCA subgroup of mCRPC patients⁵. The ESC noted that results from the second interim analysis of the MAGNITUDE trial had been published⁶ and considered that as the MAGNITUDE trial stratified patients by BRCA1/2 status, which reduced the risk of bias, a sensitivity analysis using the updated results would be informative (updated rPFS HR = 0.55; 95% CI: 0.39, 0.78 and updated OS HR = 0.54; 95% CI: 0.33, 0.90 – see Table 12).

6.64 Health state utilities were based on data from the ITT population of PROpel. This may not be reasonable since the BRCA1/2 subgroup may potentially have lower HRQoL scores and utility values due to their poorer prognosis. The utilities used in the model (PF=0.82, PD=0.78) were higher than previous utility values presented to the PBAC in

⁵ https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf, accessed: 21 Sep. 2023.

⁶ Chi KM, Sandhu S, Smith MR, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. *Annals of Oncology*. 2023;34(9):772-782

advanced prostate cancer. The PBAC had considered lower utility values for apalutamide in mHSPC; 0.79 and 0.81 for high and low-volume disease in the PF state, respectively, and 0.68 and 0.70 for high and low volume disease in PD (i.e. mCRPC) (Table 9, apalutamide PSD, July 2022). Similarly, in the darolutamide submission in mCRPC, the ESC advised a utility of 0.635 may be reflective of the total time spent in the mCRPC state (paragraph 6.43, darolutamide PSD, March 2021). The ESC considered that better justification of the utility values applied in the model was required.

- 6.65 EQ-5D-3L responses were predicted from EQ-5D-5L responses to derive utility values. The submission did not explain why the Australian value set for the EQ-5D-5L⁷ was not used to derive utility values. It has been noted⁸ that mapping EQ-5D-5L to EQ-5D-3L places an artificial floor effect on the values of EQ-5D-5L, and utilities derived directly from the EQ-5D-5L might be lower than values obtained indirectly from the EQ-5D-3L.
- 6.66 Costs applied in the model were reasonably estimated. However, the DPMQ used in the model was slightly higher than that proposed in the requested listing (\$ | versus \$|). The submission was also inconsistent in its estimation of the effective DPMQ for abiraterone across different sections of the submission, including the 5% 10-year anniversary reduction for abiraterone in the economic model but excluding it in the financials. Additionally, the cost of chemotherapy administration (for cabazitaxel and docetaxel) was inappropriately not included in either the economic or financial models.
- 6.67 Key drivers of the model are described in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
OS benefit	The submission extrapolated rPFS and OS KM data from the BRCA1/2 subgroup. In the model 20% of olaparib plus abiraterone patients remained alive at 15 years. There was high uncertainty around the magnitude of the treatment effect due to OS data immaturity, the small number of patients in the BRCA1/2 subgroup and imbalanced baseline characteristics.	High, favours olaparib plus abiraterone
Time horizon	The submission used a 15-year time horizon. However, given the uncertainty surrounding the OS data and previous PBAC recommendations, a shorter time-horizon may be more appropriate.	High, favours olaparib plus abiraterone
Time on treatment	ToT estimates were very uncertain due to 1) unclear source, 2) ToT extended beyond PFS in the NHA arm, 3) extrapolation was based on visual fit only, and 4) poor external validation against PBS utilisations for enzalutamide and abiraterone.	Moderate, favours olaparib plus abiraterone

Source: compiled during the evaluation

Cx=comparator, HR=hazard ratio, ICER=incremental cost-effectiveness ratio, NHA= novel hormonal agent, OS=overall survival, rPFS=radiological progression-free survival, PH=proportional hazard, ToT=time on treatment, Tx=treatment

⁷ Norman R. et al. The Use of a Discrete Choice Experiment Including Both Duration and Dead for the Development of an EQ-5D-5L Value Set for Australia. *Pharmacoeconomics*. 2023 Apr;41(4):427-38.

⁸ Interim value sets for the EQ-5D-5L. 2017. Accessed on 01/08/2023: https://euroqol.org/wp-content/uploads/2017/02/EQ-5D-5L_Crosswalk_model_and__methodology.pdf

6.68 The results of the stepped analysis are presented in Table 11. The results of the revised base case provided in the pre-PBAC response (time horizon of 10 years, Weibull distributions applied for all extrapolations and 1% reduction to the olaparib DPMQ) are also presented.

Table 11: Results of the stepped economic evaluation

Step and component	Olaparib plus abiraterone	NHA monotherapy	Increment
Step 1: Trial-based analysis over a 36-month time horizon (median follow-up from PROpel)			
Costs		\$52,580	
LY	2.440	1.907	0.533
Incremental cost/extra LY gained			¹
Step 2: Extrapolated analysis over 15-year time horizon, presented as cost per life year.			
Costs		\$63,221	
LY	5.870	2.397	3.474
Incremental cost/extra LY gained			²
Step 3: Extrapolated analysis over 15-year time horizon, presented as cost per QALY			
Costs (all costs, discounted)		\$63,221	
LY	5.870	2.397	3.474
Incremental discounted cost/extra LY gained (base case)			²
QALY	4.667	1.873	2.794
Incremental discounted cost/extra QALY gained			³
Pre-PBAC revised base case			
Incremental discounted cost/extra QALY gained			^{3*}

Source: Table 3-26, p149 of the submission and compiled during the evaluation

LY=life year; NHA= novel hormonal agent, QALY=quality adjusted life year

Note: numbers have been rounded.

* This ICER could not be reproduced. Reducing the time horizon to 10 years, using an AEMP of \$ [redacted] for 56 tablets (\$ [redacted] for 112 tablets) and changing all extrapolations in both arms to Weibull distributions resulted in an ICER of \$55,000 to < \$75,000 per QALY. Changing all extrapolations in the olaparib arm only to Weibull distributions resulted in an ICER of \$55,000 to < \$75,000 .

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$45,000 to < \$55,000

³ \$55,000 to < \$75,000

6.69 The estimated base case ICER for the proposed scenario (olaparib plus abiraterone) versus current scenario (NHA monotherapy) was \$55,000 to < \$75,000 per QALY gained. This ICER might not accurately reflect the cost-utility of olaparib plus abiraterone in mCRPC patients with BRCA1/2 pathogenic variants for the following reasons:

- The proposed 15-year horizon was not appropriate given the poor prognosis of BRCA1/2-positive patients, the immature OS data, and previous PBAC recommendations of shorter time-horizons in advanced prostate cancer. The ESC recommended a time horizon of 7.5 years with convergence of the OS curves.
- The PFS and OS data in the BRCA1/2 subgroup in PROpel were highly uncertain given small patient numbers and imbalanced baseline characteristics that biased the survival outcomes in favour of olaparib + abiraterone combination therapy;
- Utility values were derived from EQ-5D-5L data in the ITT population and mapped to EQ-5D-3L instead of using the EQ-5D-5L Australian value set. Overall, these

values were likely overestimated. Time to death disutility was not applied, despite the inclusion of costs for terminal illness.

6.70 The results of key univariate and multivariate sensitivity analyses are summarised in Table 12.

Table 12: Key sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% Change to ICER
Base case	█	2.79	█ ¹	-
Time horizon (base case 15 years)				
7.5 years	█	1.76	█ ²	+ █%
10 years	█	2.24	█ ¹	+ █%
Efficacy using alternate HRs for OS and PFS (base case: based on independently fitted and extrapolated KM data from PROpel)				
PROpel-reported PFS HR: 0.23 and OS HR: 0.29	█	2.77	█ ¹	█%
PROpel-reported PFS HR: 0.23 and no OS benefits (HR=1)	█	0.10	█ ³	+ █%
MAGNITUDE-reported PFS HR: 0.53 and OS HR: 0.96 (1 st interim analysis)	█	0.14	█ ³	+ █%
MAGNITUDE-reported PFS HR: 0.55 and OS HR: 0.54 (2 nd interim analysis)	█	1.49	█ ⁴	+ █%
PROpel-reported PFS HR: 0.23 and MAGNITUDE-reported OS HR: 0.54 (2 nd interim analysis)	█	1.55	█ ⁴	+ █%
Treatment duration (base case: based on ToT)				
Based on PFS	█	2.79	█ ²	+ █%
ToT extrapolation (base case: exponential)				
Best fit ToT, Tx=log-normal & Cx=log-logistic	█	2.79	█ ¹	+ █%
PFS & OS extrapolations (base case: PFS, log-normal both arms - OS, OLA+ABI exponential and NHA log-logistic)				
PFS: both Weibull (conservative PFS)	█	2.77	█ ¹	█%
OS, both Weibull (conservative OS)	█	2.61	█ ¹	█%
Utilities (base case PF: 0.82, PD: 0.78)				
PROpel utilities (Lower 95% CI) PF: 0.803, PD: 0.778	█	2.76	█ ¹	█%
PROfound pre-progression utility (0.73), for model's PD state	█	2.76	█ ¹	█%
Olaparib cost (base case DPMQ: \$ █)				
Corrected DPMQ: \$ █	█	2.79	█ ¹	- █%
Abiraterone cost (base case assumed the 5% 10-year anniversary price reduction)				
Abiraterone cost (removed 5% 10 yr anniversary reduction)	█	2.79	█ ¹	█%
Discount rate (base case: 5% for costs and QALYs)				
0% for costs and QALYs	█	3.93	█ ⁵	- █%
3.5% for costs and QALYs	█	3.08	█ ¹	- █%
Multivariate analyses (time horizon, OS benefits)				
Time horizon of 7.5 years and MAGNITUDE-reported HRs for PFS: 0.55 and OS: 0.54 (2 nd interim analysis)	█	0.82	█ ⁶	+ █%
Time horizon of 7.5 years, PROpel-reported HR PFS: 0.23 and MAGNITUDE-reported HR OS: 0.54 (2 nd interim analysis)	█	0.87	█ ⁶	+ █%

Source: Table 3-30, p153 and compiled during the submission

Cx=comparator, DPMQ=dispensed price for maximum quantity, HR=hazard ratio, ICER=incremental cost-effectiveness ratio, OS=overall survival, QALY=quality-adjusted life year, PD=progressed disease, PF=progression-free, PFS=progression-free survival, ToT=time on treatment, Tx=treatment.

^a In the base case, transition probabilities for each health state were calculated based on the PFS and OS curves from PROpel, independently fitted to each treatment.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ > \$1,055,000

⁴ \$95,000 to < \$115,000

⁵ \$45,000 to < \$55,000

⁶ \$155,000 to < \$255,000

6.71 Sensitivity analyses demonstrated the model was most sensitive to time horizon, OS benefit, and ToT, noting that the current model structure did not allow testing of convergence assumptions.

Drug cost/patient/course: \$ [REDACTED] (assuming a treatment duration of 1,261 days or 3.45 years)

6.72 Table 13 outlines the drug cost per patient for both olaparib plus abiraterone and NHA monotherapy across the model and the financial estimates at the price proposed in the submission (DPMQ = \$ [REDACTED]).

Table 13: Drug cost per patient (BRCA1/2 subgroup) for proposed and comparator drugs

	Olaparib plus abiraterone			NHA monotherapy		
	Trial dose / duration	Model	Financial estimates	Trial dose / duration	Model	Financial estimates
Mean dose	OLA: 600mg/day, ABI: 1000mg/day, Pred: 10mg/day			ABI:1000mg/day, Pred:10mg/day, ENZ:160mg/day		
Mean treatment duration (days)	NR ^a	1,261 days	1,261 days	NR ^a	433 days	433 days
Total mg administered	NC	OLA ^b : 693,802 mg ABI ^b : 1,214,343 mg	OLA ^c : 696,072 mg ABI ^c : 1,223,170 mg	NC	ABI: 416,979 mg ENZ: 66,716 mg	ABI: 420,010 mg ENZ: 67,202 mg
Cost/patient/month	NR	OLA: \$ [REDACTED] ABI+ Pred: \$ [REDACTED] Total: \$ [REDACTED]	NR	NR	ABI+Pred: \$1,278.84 ENZ: \$1,329.60 Mean ^d : \$1,310.82	NR
Cost/patient/course	NR	\$ [REDACTED]	\$ [REDACTED] ^{e, f}	NR	\$18,582	

Source: Table 3-16, p140, Table 3-25, p148 of the submission and compiled during the evaluation

ABI=abiraterone, BRCA=breast cancer gene, cc=concomitant therapies, ENZ=enzalutamide, NC=not calculatable, NR=not reported, OLA=olaparib, Pred=methylprednisolone, NHA= novel hormonal agents.

^a The submission did not present treatment duration or discontinuations in the BRCA1/2 subgroup of PROpel

^b A dose intensity of 91.7% for olaparib and 96.3% for abiraterone and enzalutamide was applied in the economic model.

^c A dose intensity of 92.0% for olaparib and 97.0% for abiraterone and enzalutamide was applied in the financial estimates.

^d The submission assumed that 37% of patients would take abiraterone, and 63% would take enzalutamide.

^e This was calculated based on the PBS/RPBS net cost of patients treated in Year 1, divided by the number of patients initiating and continuing treatment (116). Co-payment cost has been subtracted.

^f The difference in cost/patient/course between the model and the financial estimates may be due to some disparities, including the applied dose intensity and abiraterone's DPMQ (financial estimates did not include the 5% anniversary price reduction)

6.73 The cost per patient per course of treatment was derived from the mean dose and mean treatment duration in the BRCA1/2 subgroup in the economic model. The submission did not report mean treatment duration for the BRCA1/2 subgroup.

Estimated PBS usage & financial implications

6.74 This submission was not considered by DUSC.

6.75 An epidemiological approach was used to determine the number of mCRPC patients with BRCA1/2 mutations who would be eligible for treatment. Table 14 summarises the parameters and data sources applied in the financial analysis.

Table 14: Key inputs for financial estimates

Parameter	Value applied and source	Comment																					
Incident population																							
Incident patients (based on total NHA initiations in 1L mCRPC)	<table border="1"> <thead> <tr> <th>2024</th> <th>2025</th> <th>2026</th> <th>2027</th> <th>2028</th> <th>2029</th> </tr> </thead> <tbody> <tr> <td>█¹</td> <td>█¹</td> <td>█¹</td> <td>█¹</td> <td>█²</td> <td>█²</td> </tr> </tbody> </table>	2024	2025	2026	2027	2028	2029	█ ¹	█ ¹	█ ¹	█ ¹	█ ²	█ ²	Likely underestimated; as 2020 data, which is likely to be affected by COVID-19, was included in the NHA initiation calculation. Using NHA initiations from 2016-2019 and a decreased growth rate of 3.9% (as applied as a sensitivity analysis in the olaparib monotherapy submission) increased the 6-year budget by 11.5% to \$ █ ³ , from a base case of \$ █ ⁴ .									
	2024	2025	2026	2027	2028	2029																	
█ ¹	█ ¹	█ ¹	█ ¹	█ ²	█ ²																		
Incident population were calculated using NHA initiations 2016-2020 from 10% PBS sample with average annual growth rate (6.86%). These were as used in the previous olaparib submission for 2L mCPRC (Table 16, olaparib, PBAC Minutes, November 2021).																							
NHA-naïve mCRPC patients	<table border="1"> <thead> <tr> <th>Year</th> <th>2024</th> <th>2025</th> <th>2026</th> <th>2027</th> <th>2028</th> <th>2029</th> </tr> </thead> <tbody> <tr> <td>%</td> <td>52%</td> <td>47%</td> <td>43%</td> <td>43%</td> <td>43%</td> <td>43%</td> </tr> <tr> <td>N</td> <td>█¹</td> <td>█¹</td> <td>█¹</td> <td>█¹</td> <td>█¹</td> <td>█¹</td> </tr> </tbody> </table>	Year	2024	2025	2026	2027	2028	2029	%	52%	47%	43%	43%	43%	43%	N	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	Likely overestimated the proportion of NHA-naïve patients. The ESC considered that with the recent PBS listing of apalutamide, enzalutamide and darolutamide earlier in the treatment pathway for mHSPC and m0CRPC, the number of NHA-naïve mCPRC patients would be expected to decrease over the forward estimates. The proportion of NHA-naïve patients was decreased in the pre-PBAC response from Year 3 onwards from 43% to 38%.
	Year	2024	2025	2026	2027	2028	2029																
	%	52%	47%	43%	43%	43%	43%																
N	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹																	
NHA-naïve patients were estimated in two steps: i) based on the proportion of patients who progressed from m0HSPC, mHSPC, and m0CRPC to mCRPC (sourced from Sweden registry ⁹); and ii) the proportion of NHA-naïve patients was calculated from the estimated proportions of patients accessing PBS-funded NHAs for each stage of disease (derived from apalutamide PSDs for mHSPC and m0CRPC and assuming 100% m0HSPC patients that develop mCRPC are NHA naïve due to no PBS listed NHAs in this setting).																							
BRCA1/2 positive, NHA-naïve, mCRPC patients (eligible)	<table border="1"> <thead> <tr> <th>2024</th> <th>2025</th> <th>2026</th> <th>2027</th> <th>2028</th> <th>2029</th> </tr> </thead> <tbody> <tr> <td>█⁵</td> <td>█⁵</td> <td>█⁵</td> <td>█⁵</td> <td>█⁵</td> <td>█⁵</td> </tr> </tbody> </table> <p>90% BRCA1/2 test uptake and 7% prevalence rates were sourced from the olaparib PSD (para 4.4, olaparib, PSD, November 2021)</p>	2024	2025	2026	2027	2028	2029	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	BRCA test uptake and prevalence rates were appropriate.									
2024	2025	2026	2027	2028	2029																		
█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵																		
Treated patients																							
Uptake and continuation rate	<table border="1"> <thead> <tr> <th>2024</th> <th>2025</th> <th>2026</th> <th>2027</th> <th>2028</th> <th>2029</th> </tr> </thead> <tbody> <tr> <td>█⁵</td> <td>█⁵</td> <td>█⁵</td> <td>█⁵</td> <td>█⁵</td> <td>█⁵</td> </tr> </tbody> </table>	2024	2025	2026	2027	2028	2029	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	Calculations were correct. A 100% treatment continuation was justified because discontinuations were already accounted for in the ToT data. Further discussion below.									
	2024	2025	2026	2027	2028	2029																	
█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵																		
Uptake of █% and continuation rate of 100% across Years 1 to 6 was a submission assumption. No grandfathered or prevalent patients were included.																							
Duration of treatment & scripts dispensed	<table border="1"> <thead> <tr> <th>2024</th> <th>2025</th> <th>2026</th> <th>2027</th> <th>2028</th> <th>2029</th> </tr> </thead> <tbody> <tr> <td>█¹</td> <td>█²</td> <td>█²</td> <td>█²</td> <td>█²</td> <td>█⁶</td> </tr> </tbody> </table>	2024	2025	2026	2027	2028	2029	█ ¹	█ ²	█ ²	█ ²	█ ²	█ ⁶	The source of ToT in the BRCA1/2 subgroup could not be verified. ToT extrapolated data were used to estimate mean ToT. The duration of NHA monotherapy was reduced to 359.2 days (11.8 months) in the pre-PBAC response. The duration of OLA plus ABI was adjusted to align with the revised economic model.									
	2024	2025	2026	2027	2028	2029																	
█ ¹	█ ²	█ ²	█ ²	█ ²	█ ⁶																		
The treatment duration for olaparib and NHA was sourced from the extrapolated ToT curves reported in the economic model. ToT for OLA plus ABI: 1,261 days, NHA: 433.5 days. Dose intensity was 92% for olaparib, and 97% for NHA, as per ITT data in PROpel. Scripts per course of OLA+ABI treatment per patient: OLA: 41.43, ABI: 40.77																							

⁹ Svensson J et al. Time spent in hormone-sensitive and castration-resistant disease states in men with advanced prostate cancer, and its health economic impact: registry-based study in Sweden. Scand J Urol. 2021 Feb;55(1):1-8.

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Parameter	Value applied and source	Comment												
Concomitant treatments	MP was assumed to be dispensed with ABI, as part of the Yonsa MPRED® formulation.	This was consistent with the economic model.												
Reduction in numbers of patients initiating subsequent olaparib in 2L	<table border="1"> <thead> <tr> <th>2024</th> <th>2025</th> <th>2026</th> <th>2027</th> <th>2028</th> <th>2029</th> </tr> </thead> <tbody> <tr> <td>█⁵</td> <td>- █⁵</td> <td>- █⁵</td> <td>- █⁵</td> <td>- █⁵</td> <td>- █⁵</td> </tr> </tbody> </table> <p>Calculated from the eligible population and assuming 80% disease progression rate (Table 16, olaparib, PBAC minutes, November 2021) and olaparib uptake rate in 2L of 95% (Table 16, Olaparib, PSD, November 2021). Mean duration of treatment 332 days from Table 15, PSD, olaparib, November 2021.</p>	2024	2025	2026	2027	2028	2029	█ ⁵	- █ ⁵	- █ ⁵	- █ ⁵	- █ ⁵	- █ ⁵	No other subsequent treatments were costed in the financial estimates. This was inconsistent with the economic model, in which cabazitaxel and docetaxel-based subsequent therapies and their administration costs were included.
2024	2025	2026	2027	2028	2029									
█ ⁵	- █ ⁵	- █ ⁵	- █ ⁵	- █ ⁵	- █ ⁵									
Reduction in numbers of patients initiating ABI and ENZA monotherapy	<table border="1"> <thead> <tr> <th>2024</th> <th>2025</th> <th>2026</th> <th>2027</th> <th>2028</th> <th>2029</th> </tr> </thead> <tbody> <tr> <td>- █⁵</td> <td>- █⁵</td> <td>- █⁵</td> <td>- █⁵</td> <td>- █⁵</td> <td>- █⁵</td> </tr> </tbody> </table> <p>Assuming 37% ABI and 63% ENZA share (10% PBS Sample) and based on mean duration of treatment of 433 days (14.3 months) as estimated from Section 3.</p>	2024	2025	2026	2027	2028	2029	- █ ⁵	- █ ⁵	- █ ⁵	- █ ⁵	- █ ⁵	- █ ⁵	This was consistent with the economic model. However, the duration of treatment for ABI and ENZA may be overestimated. A recent DUSC analysis in April 2022 suggested the average PBS treatment durations for abiraterone and enzalutamide were 9 and 12 months respectively or 11.8 months combined (assuming zero treatment breaks). However, the DUSC estimates were not specific to a BRCA1/2 population (para 6.26, apalutamide, PSD, July 2022). The ESC considered that NHA monotherapy would potentially be shorter than 11.8 months as patients with BRCA1/2 mutation are less responsive to NHAs.
2024	2025	2026	2027	2028	2029									
- █ ⁵	- █ ⁵	- █ ⁵	- █ ⁵	- █ ⁵	- █ ⁵									
PBS/RPBS Costs (DPMQ, effective)														
Olaparib	OLA: \$ █ per 28-day supply (requested effective DPMQ)	DPMQ for olaparib was slightly higher than the actual DPMQ requested in Section 1 (\$█). This was reduced to \$█ in the pre-PBAC response.												
ABI	ABI: \$1,356.21 per 30-day supply (sponsor's assumption) Note MP cost (\$3.39) was not included in the model. This had minimal impact.	Some discrepancies were noted between the economic model and financial estimates: <ul style="list-style-type: none"> The economic model factored in a 5% anniversary-related price reduction for abiraterone, which was absent from the financial analysis. Olaparib's dose intensity was 91.7% (economic) vs. 92% (financial), and for NHA it was 96.3% (economic) vs. 97% (financial). 												
NHA monotherapy	ABI: \$1,356.21 per 30-day supply (sponsor's assumption) ENZA: \$1,270.12 per 30-day supply (sponsor's assumption)													
PBS/RPBS split	PBS=95.8% & RPBS=4.2%, based on existing PBS/RPBS Item statistics for ABI and ENZA in 1L mCRPC	The split was consistent with PBS data for olaparib monotherapy (item 12929L, 95.98% / 4.02%).												
Patient co-payment	PBS=\$9.93 & RPBS=\$4.93 Average co-payment, for both drugs, was based on the current weighted mean co-payment of abiraterone and enzalutamide	-												

Source: Table 4-3, p160, Table 4-8, p163, Table 4-9, p63, Table 4-10, p164, Table 4-12, p165, Table 4-18, p168, and compiled during the evaluation.

1L=first line, 2L=second line, ABI=abiraterone, BI=budget impact, BRCA1/2=breast cancer gene, DPMQ=dispensed price for maximum quantity, m0CRPC=non-metastatic castrate resistant prostate cancer, mCRPC=metastatic castrate resistant prostate cancer, MP=methylprednisolone, NHA=novel hormonal agent, OLA=olaparib, PBS=Pharmaceutical Benefits Scheme, RPBS=Repatriation Schedule of Pharmaceutical Benefits, ToT=time on treatment.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ \$100 million to < \$200 million

⁴ \$90 million to < \$100 million

⁵ < 500

⁶ 10,000 to <20,000

- 6.76 Only incident patients were included, which was a deviation from the preferred approach recommended by DUSC of a combined incident and prevalent approach. The submission explained it was expected that patients would commence treatment shortly after their mCRPC diagnosis, and as such there would not be a pool of untreated prevalent patients who would be eligible to commence treatment. The submission also indicated that there was no patient access program established at the time of submission, so no grandfathering was included in the estimates.
- 6.77 Table 15 presents the estimated use and financial impact of olaparib plus abiraterone.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Estimated extent of use							
NHA initiations in 1L mCRPC	1	1	1	1	2	2	3
NHA-naïve patients	1	1	1	1	1	1	4
BRCA1/2-positive patients	5	5	5	5	5	5	2
Number of patients treated	5	5	5	5	5	5	2
Number of scripts dispensed ^a	1	2	2	2	2	4	6
Estimated financial implications of olaparib plus abiraterone							
Net cost to PBS/RPBS	7	8	9	9	9	9	10
Estimation changes in financial impact of currently listed treatments^b							
Cost offsets for NHAs (ABI+ENZA)	11	11	11	11	11	11	11
Cost offsets for OLA (2L)	7	11	11	11	11	11	11
Net cost offsets to PBS/RPBS	11	11	11	11	11	11	11
Net financial implications							
Net cost to PBS/RPBS	7	7	8	9	9	9	12
Net cost to MBS ^c	7	7	7	7	7	7	7
Net change to health budget	7	7	8	9	9	9	12
Pre-PBAC revised net financial implications							
Net cost to PBS/RPBS	7	7	8	8	8	8	13

Source: Table 4-3, p160, Table 4-8, p163, Table 4-10, p164, Table 4-13, p166, Table 4-21, p169, Table 4-27, p174, Table 4-29, p175, and Table 4-33, p177, and compiled during the evaluation

1L=first line, 2L=second line, ABI=abiraterone, BRCA=breast cancer gene, ENZA=enzalutamide, MBS=Medicare Benefits Schedule, mCRPC=metastatic castrate resistant prostate cancer, NHA=novel hormonal agent, OLA=olaparib, PBS=Pharmaceutical Benefits Scheme, RPBS=Repatriation Schedule of Pharmaceutical Benefits

^a Calculated, assuming 12 olaparib and 11.81 abiraterone scripts per patient per year, for the treatment duration (based on mean extrapolated ToT).

^b This includes changes to the number of abiraterone, enzalutamide and olaparib monotherapy (2L mCRPC) scripts.

^c This could have included the cost of administration of the affected subsequent chemotherapies, including docetaxel and cabazitaxel.

The redacted values correspond to the following ranges:

- ¹ 500 to < 5,000
- ² 5,000 to < 10,000
- ³ 20,000 to < 30,000
- ⁴ 10,000 to < 20,000
- ⁵ < 500
- ⁶ 40,000 to < 50,000
- ⁷ \$0 to < \$10 million
- ⁸ \$10 million to < \$20 million
- ⁹ \$20 million to < \$30 million
- ¹⁰ \$100 million to < \$200 million
- ¹¹ net cost saving
- ¹² \$90 million to < \$100 million
- ¹³ \$80 million to < \$90 million

6.78 The total cost to the PBS/RPBS of listing olaparib plus abiraterone was estimated to be \$20 million to < \$30 million in Year 6, and a total of \$90 million to < \$100 million in the first 6 years of listing. This was reduced by 1% in the pre-PBAC response to \$80 million to < \$90 million over the first 6 years of listing due to the reduction in the price and to the treatment duration.

6.79 The proposed financial estimates are uncertain for the following reasons:

- ToT may be overestimated: i) Mean ToT was estimated from extrapolated Kaplan-Meier ToT data in the BRCA1/2 subgroup of PROpel, but as previously mentioned

the source of these data was unclear; ii) the submission assumed that both initiating and ongoing patients had the same mean treatment duration each year. This may not be clinically plausible as continuing patients may discontinue earlier than incident patients, given they have received treatment for longer and are more likely to progress due to longer disease duration.

- The projected NHA uptake in earlier treatment stages was likely underestimated, particularly in mHSPC. The ESC considered that the estimate that 43% of mCRPC patients would be NHA naïve in Years 3 to 6 was high and that it led to an overestimation of NHA-naïve patients at mCRPC stage. Projected NHA use in first line mCRPC may also be underestimated. The ESC considered that the number of NHA-naïve patients in the mCRPC setting would likely decrease over the forward estimates. The ESC noted that a sensitivity analysis in which the uptake of NHAs in prior lines of therapy was increased by 10% decreased the 6-year budget by 12% to \$80 million to < \$90 million from a base case of \$90 million to < \$100 million.
 - Cost offsets for reductions in use of enzalutamide or abiraterone monotherapy in mCRPC may be overestimated due to a likely overestimate of the mean treatment duration (14.3 months). This was higher than the DUSC analysis in April 2022 that reported an average combined treatment duration for abiraterone and enzalutamide of 11.8 months on the PBS (see paragraph 6.54). Using 11.8 months as mean ToT for NHAs decreased the cost offset and increased the 6-year budget by 2% to \$90 million to < \$100 million. The ESC considered that NHA monotherapy duration of therapy would potentially be shorter than 11.8 months as patients with BRCA1/2 pathogenic variants are less responsive to NHAs.
 - The omission of taxane-based subsequent therapy and administration costs was inappropriate. The submission only included subsequent olaparib monotherapy in the comparator arm, which contrasts with the inclusion of docetaxel and cabazitaxel after disease progression in the economic model. Given patients who progress on olaparib plus abiraterone lack the option of subsequent olaparib monotherapy or NHAs, they are likely to be treated with taxanes. This omission is likely to lead to an underestimation of costs in patients treated with olaparib plus abiraterone. However, given the significantly lower cost of docetaxel and cabazitaxel versus olaparib and NHA, this was unlikely to be a key cost driver.
- 6.80 Overall, the net costs associated with the PBS-listing of olaparib plus abiraterone are uncertain, particularly in the latter years of the forward estimates. Given the above, the ESC considered that the PBS/RPBS cost for olaparib plus abiraterone was likely substantially overestimated as the use of NHAs earlier in the prostate cancer treatment algorithm is likely higher than estimated, thus reducing the number of NHA-naïve patients eligible for treatment in mCRPC. This may be, however, at least partially offset by the overestimation of cost offsets (driven by an overestimation of NHA treatment duration in patients with BRCA1/2 pathogenic variants on the PBS).

6.81 The financial estimates were sensitive to changes in the number of patients eligible for olaparib (including prevalence and test uptake rate of BRCA1/2 pathogenic variants, disease progression, and NHA uptake rates in earlier treatment stages), treatment duration of NHA monotherapy, progression rate following first line mCRPC NHA monotherapy, subsequent initiation of second line olaparib monotherapy and olaparib price.

Quality Use of Medicines

6.82 The submission stated that the sponsor will work collaboratively with health care professionals to ensure that olaparib is used appropriately and in line with the available clinical evidence and TGA restriction.

Financial Management – Risk Sharing Arrangements

6.83 The submission outlined the Risk Share Arrangement (RSA) for the current olaparib monotherapy restriction, effective since April 1, 2022. This includes a 1% rebate beyond the financial caps and expires on March 31, 2027. The submission also detailed the projected expenditure caps for the new olaparib combination therapy listing. It suggested creating an RSA considering the combined expenditure caps for olaparib treatment in first- and second-line settings, as illustrated in Table 16.

Table 16: Expenditure caps for olaparib in the first and second line of mCRPC therapy

	2024	2025	2026	2027	2028	2029
New listing (olaparib combination)						
Total costs (PBS/RPBS)	■	■	■	■	■	■
Olaparib offset from monotherapy						
Total costs (PBS/RPBS)	■	■	■	■	■	■
Olaparib monotherapy (current Deed) ^a						
Total costs (PBS/RPBS)	■	■	■	■	■	■
Total olaparib cost to PBS/RPBS (monotherapy and combination)						
Total costs (PBS/RPBS)	■	■	■	■	■	■

Source: Table 4-37, p180 of the submission

BIM= budget impact model, PBS=Pharmaceutical Benefits Scheme, RPBS=Repatriation Schedule of Pharmaceutical Benefits

^a Assumes timing of new olaparib combination listing align with current olaparib monotherapy Deed years. Assumes expenditure caps for olaparib monotherapy remains constant after the completion of the existing Deed Term.

6.84 The proposed RSA carries uncertainty, primarily because of the PBS listing of more NHAs in earlier disease stages (i.e., mCRPC and mHSPC), which could lead to a decrease in NHA-naïve patients in the first line mCRPC setting and an overestimate of olaparib utilisation. Moreover, uncertainties around the extrapolated ToT, especially in NHA monotherapy, also contribute to the uncertainty of the RSA.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend olaparib, for use in combination with abiraterone, for the first line treatment of metastatic castration-resistant prostate cancer (mCRPC) patients with breast cancer gene (BRCA)1/2 pathogenic variants who have not

received prior treatment with a novel hormonal agent (NHA). The PBAC considered that the clinical evidence presented in the submission, which was based on a small *post-hoc* subgroup, was uncertain. The PBAC also considered that the incremental cost effectiveness ratio (ICER) was highly uncertain and likely underestimated and that the financial impact estimates were overestimated. Further, the PBAC considered that the clinical place of olaparib in combination with abiraterone was uncertain, noting that olaparib was available as monotherapy in the mCRPC setting following treatment with a NHA and that no evidence was presented to suggest that the combination of olaparib and abiraterone was superior to sequential treatment of a NHA followed by olaparib.

- 7.2 The primary reason for this outcome was due to the comparative clinical evidence presented.
- 7.3 The PBAC noted the input from individuals and organisations which supported the submission and acknowledged that the Medical Oncology Group of Australia (MOGA) expressed its strong support for the submission.
- 7.4 The PBAC noted that the submission placed olaparib in combination with abiraterone as a first line option for mCRPC patients with BRCA1/2 pathogenic variants who had not received prior NHA treatment. The PBAC considered that use of olaparib and abiraterone in this setting would likely be low as the majority of mCRPC patients would have received NHA therapy in the metastatic hormone sensitive or non-metastatic castration resistant settings and thus, would not be eligible for treatment with the olaparib combination. Further, the PBAC noted that olaparib was available as monotherapy in the mCRPC setting following treatment with a NHA and that no evidence was presented to suggest that the combination of olaparib and abiraterone was superior to sequential treatment of a NHA followed by olaparib.
- 7.5 The PBAC noted that the submission was based on a *post hoc* subgroup analysis of the PROpel trial, which compared olaparib and abiraterone to placebo and abiraterone. The PBAC noted that the *post hoc* subgroup, which consisted of patients with BRCA1/2 pathogenic variants, was not powered to detect robust treatment differences as it was small (n = 85) compared to the intention to treat (ITT) population of the trial (N = 796). Further, as the BRCA1/2 subgroup was not pre-specified, the PBAC noted that the results should be interpreted with caution.
- 7.6 Further, the PBAC noted that randomisation was not stratified for BRCA1/2 variants, and the baseline characteristics across the two arms of the subgroup were not balanced in terms of age, percentage of visceral metastases, prior docetaxel treatment and Eastern Co-Operative Oncology Group (ECOG) performance status scores which likely biased the results in favour of olaparib and abiraterone. The PBAC noted that the PSCR presented a multivariate analysis that adjusted for potential confounders (see paragraph 6.16) but considered that due to the small sample size of the BRCA1/2 subgroup, the validity of the adjusted model was unclear, and the effects of confounding remained uncertain.
- 7.7 The PBAC noted that the MAGNITUDE trial, which compared niraparib and abiraterone

to placebo and abiraterone and which was stratified by BRCA1/2 status, reported a considerably lower magnitude of effect for rPFS and OS compared to the PROpel trial (see Table 8).

- 7.8 For the reasons outlined in paragraphs 7.5 to 7.7, the PBAC considered that, although the radiograph progression free survival (rPFS) and overall survival (OS) results favoured olaparib and abiraterone for patients with a BRCA1/2 pathogenetic variant, the magnitude of the clinical effect was highly uncertain. Further, the PBAC noted that it was unknown whether olaparib in combination with abiraterone was superior compared to the currently available sequential therapy (i.e. a NHA followed by olaparib monotherapy).
- 7.9 In terms of safety, the PBAC considered that olaparib was inferior compared to placebo, noting that olaparib was associated with increased rates of venous thromboembolism.
- 7.10 As the magnitude of the clinical benefit in patients with a BRCA1/2 pathogenic variant was uncertain, the PBAC considered that the economic model was highly uncertain and that the base case ICER was likely underestimated. The PBAC considered that, for the model presented in the submission, the:
- 15-year time horizon was too long given the poor prognosis of patients with BRCA1/2 pathogenetic variants, and the limited data presented in the submission. Additionally, the 15-year time horizon was not consistent with previous PBAC recommendations in advanced prostate cancer (see paragraphs 6.49 and 6.50);
 - extrapolations which resulted in 20% of patients in the olaparib and abiraterone arm remaining alive at 15 years were not clinically plausible (see paragraph 6.60); and
 - utilities applied in the model, which were based on the ITT population of PROpel, were high compared to previous utility values presented to the PBAC in the advanced prostate cancer setting (see paragraphs 6.64 and 6.65).
- 7.11 In terms of the financial impact, the PBAC noted that the changes proposed in the pre-PBAC response reduced the estimated cost of listing olaparib on the PBS/RPBS from \$90 million to < \$100 million to \$80 million to < \$90 million over the first 6 years. The PBAC considered that the estimated cost was overestimated as the proportion of mCRPC patients who were NHA naïve was significantly overestimated in both the submission and the pre-PBAC response (52% in Year 1 decreasing to 43% from Year 3 onwards in the submission and to 38% in the pre-PBAC response). The PBAC considered that there were additional uncertainties in the utilisation and financial impact estimates as outlined in Table 14.
- 7.12 The PBAC considered any resubmission should address the clinical role of olaparib and abiraterone, including any benefit over sequential use, and that further clinical evidence would be required. A resubmission should also address the issues identified during the evaluation process relating to the economic model and financial forecasts.

The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway. The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.