

6.08 OLAPARIB, Tablet 100 mg, Tablet 150 mg Lynparza® AstraZeneca Pty Ltd

1 Purpose of submission

- 1.1 The submission requested MBS listing of *BRCA1/2* pathogenic gene variant testing and PBS listing of olaparib for the targeted treatment of metastatic castration resistant prostate cancer (mCRPC).
- 1.2 Listing was requested on the basis of a cost-utility analysis versus either abiraterone or enzalutamide as novel hormonal agents (NHAs). The key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	<u>Test</u> : Patients diagnosed with metastatic castration-resistant prostate cancer (mCRPC). <u>Medicine</u> : Patients with mCRPC who have failed first- or second-line physician choice of NHA treatment and have pathogenic or likely pathogenic <i>BRCA1/2</i> gene variants in tumour tissue.
Intervention	<u>Test</u> : Testing of metastatic tumour tissue to detect pathogenic <i>BRCA1/2</i> gene variants, or use of germline testing if tumour testing is not feasible, to determine eligibility for olaparib; germline <i>BRCA</i> testing will be offered to patients when a pathogenic or likely pathogenic gene variant has been identified in a tumour tissue test. <u>Medicine</u> : Olaparib 300 mg (2×150 mg) twice daily (total dose 600 mg/day) for patients found to be positive for a selected <i>BRCA1/2</i> gene variant after failed treatment with physician's choice of NHA.
Comparator	<u>Test</u> : No genetic testing. <u>Medicine</u> : physician's choice of NHA in both second- and third-line patients.
Outcomes	OS, PFS, health-related QoL, AEs (drug and test), analytical and clinical validity of test.
Clinical claim	For patients diagnosed with mCRPC who have failed first- or second-line NHA treatment and have a pathogenic or likely pathogenic <i>BRCA1/2</i> gene variant in tumour tissue or the germline, olaparib is superior in efficacy. Safety and tolerability in this population is consistent with the known safety and tolerability profile of olaparib.

Source: Table 1-1, p24 of the submission.

AE = adverse event; *BRCA1/2* = breast cancer genes 1 and 2; mCRPC = metastatic castration-resistant prostate cancer; NHA = novel hormonal agent; OS = overall survival; PFS = progression-free survival; QoL = quality of life.

- 1.3 The submission proposed that a diagnostic test to identify *BRCA1/2* pathogenic gene variants occur at diagnosis of mCRPC, with olaparib used as a second- or later-line treatment option for mCRPC in patients who have failed NHA treatment (i.e. enzalutamide or abiraterone). There is no medicine explicitly available on the PBS for this specific patient population whether or not the patient has a *BRCA1/2* variant.

Claim of codependence

- 1.4 The submission claimed that identification of *BRCA* gene variants in patients with mCRPC could optimise treatment in these patients, through access to a targeted therapy and by prolonging survival in this population. However, all patients in the key trial, the PROfound trial, had pathogenic gene variants and no comparisons were provided against patients without the biomarker.
- 1.5 The ESCs concluded that there was sufficient indirect evidence to support the clinical utility of *BRCA1/2* testing in the proposed population. The ESCs considered the PROfound trial reported a clinically meaningful improvement in overall survival (OS) for the *BRCA1/2* subgroup that was not seen for other pathogenic variants of other HRR genes. Additionally, the ESCs noted that the Phase II TOPARP-B study of olaparib also showed a greater response in the *BRCA1/2* subgroup than other genetic variants. The ESCs noted that, although there was no direct evidence of clinical utility, the evidence suggested olaparib was not as effective in non-*BRCA* HRR genetic variants.

2 Background

Registration status

- 2.1 An application to the TGA to extend the registration of olaparib to include patients with mCRPC and a detected pathogenic gene variant was made on 29th February 2020. The requested indication was:

Treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair (HRR) gene mutation [variants] (germline and/or somatic) who have progressed following a prior new [novel] hormonal agent. HRR gene mutation [variant] status should be determined by an experienced laboratory using a validated test method.
- 2.2 Olaparib received approval from the FDA on 19th May 2020 for treatment of adult patients with germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone. In Canada, olaparib was approved in August 2020 for treatment of adults with deleterious or suspected deleterious germline and or somatic *BRCA* or *ATM* mutated mCRPC who have progressed following prior treatment with an NHA.
- 2.3 The European Medicines Agency (EMA) granted marketing authorisation in November 2020 for the use of olaparib for treatment of adult patients with mCRPC and *BRCA1/2* pathogenic variants (germline or somatic) who have progressed following prior therapy that includes an NHA.
- 2.4 The TGA Delegate's overview (dated 4 Jan 2021) was received during the evaluation, and the Delegate's recommendation was to approve the registration of olaparib, with

a limitation of the indication to patients with *BRCA1* or *BRCA2* pathogenic variants. The TGA Delegate explained that exploratory analyses of progression free survival (PFS) and OS in the *ATM* and *CDK12* subgroups within PROfound do not support a conclusion of meaningful efficacy in these groups, over the comparator. The TGA Delegate concluded that the presence of a *non-BRCA* HRR pathogenic variant is not considered a biomarker that sufficiently predicts for response on a population level to justify exposing this population to the additional toxicity that is conferred by treatment with olaparib compared to an NHA. Efficacy in the *BRCA1/2* group was mainly driven by results in patients with *BRCA2*; however, the delegate felt grouping of *BRCA1* and *BRCA2* was reasonable given the breadth and strength of pre-clinical and clinical evidence of sensitivity of PARP inhibitors in *BRCA1* and *BRCA2* pathogenic variants. It was noted, that like other rarer mutations, the relative low rate of *BRCA1* pathogenic variants in prostate cancer makes it difficult to assess responses in *BRCA1* population independent of *BRCA2*.

- 2.5 The pre-PBAC response stated that a revised TGA Delegate’s overview (dated 16 Feb 2021) proposed the following indication for olaparib:

Treatment of adult patients with *BRCA*-mutated (germline and/or somatic) metastatic castration resistant prostate cancer who have progressed following prior therapy that included a new hormonal agent. *BRCA* mutation status should be determined by an experienced laboratory using a validated test method.

Previous PBAC consideration

- 2.6 There have been no previous PBAC considerations of olaparib for treatment of mCRPC, but there have been a number of submissions for the use of olaparib in ovarian cancer.

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

3 Requested listing

Proposed PBS listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
OLAPARIB, tablet, 150mg, 100mg, 56 Initial treatment	2	112	2	\$6,986.96 (published) \$ [REDACTED] (effective)	LYNPARZA® AstraZeneca Pty Ltd
OLAPARIB, tablet, 150mg, 100mg, 56 Continuing treatment	2	112	5	\$6,986.96 (published) \$ [REDACTED] (effective)	LYNPARZA® AstraZeneca Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☒ Medical Practitioners
Severity:	Metastatic
Condition:	Carcinoma of the prostate
PBS Indication:	Castration resistant metastatic carcinoma of the prostate
Treatment phase:	Initial
Restriction Level / Method:	☒ Authority Required – Telephone/Electronic/Emergency
Clinical criteria:	Patient must have homologous recombination repair gene variants (germline and/or somatic) <i>BRCA1</i> or <i>BRCA2</i> AND The treatment must not be used in combination with chemotherapy or novel hormonal agents AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug AND Patient must have progressed or failed treatment following a prior novel hormonal agent treatment OR Patient must be unsuitable for novel hormonal agent treatment on the basis of predicted intolerance AND Patient must have a WHO performance status of 2 or less AND Patient must not have received prior treatment with olaparib
Treatment phase:	Continuing
Restriction Level / Method:	☒ Authority Required – Telephone/Electronic/Emergency ☒ Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug
Administrative Advice:	Special Pricing Arrangements apply

Source: Table 1-10, p54-55, Table 1-11, p55-56 of the submission.

- 3.1 Olaparib is proposed to be used as monotherapy following progression with NHA treatment. The recommended dose is 300 mg (2×150 mg tablets) twice daily, for a total of 600 mg/day, until progression.

- 3.2 The requested restriction, which specifies that patients must have *BRCA1* or *BRCA2* pathogenic gene variants, is consistent with the TGA delegate's recommendation.
- 3.3 The requested restriction uses similar wording to that used in the PBS listings of abiraterone and enzalutamide for treatment of mCRPC, but instead of specifying that patients have failed treatment or are intolerant to docetaxel, the requested listing specifies that patients have failed or are intolerant to novel hormonal agents, e.g. abiraterone and enzalutamide.

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

4 Population and disease

- 4.1 mCRPC is an incurable disease with a substantial impact on patients' survival. One strategy for treating mCRPC relies on targeting tumours that are deficient in homologous recombination DNA repair (HRR). The altered genes that are responsible for producing deficient HRR include *BRCA1*, *BRCA2*, *PALB2*, and *RAD51D*, other HRR genes, such as *ATM*, *CHEK2*, and *FANCA* are important as they indirectly interact with the HRR protein complex. The poly ADP-ribose polymerase (PARP) enzyme fixes DNA damage in both healthy and cancer cells. Cancer cells with pathogenic variants in HRR genes have defective HRR function, and the unrepaired DNA breaks that result after treatment with PARP inhibitors eventually lead to cancer cell death. This process is referred to as "synthetic lethality," in which two conditions that would independently not cause cell death, when present in combination cause lethal injury to the cancer cell. The available evidence suggests that response rates to PARP inhibitors are highest in those with germline or somatic *BRCA1/2* genetic variants.
- 4.2 The submission has proposed that a diagnostic test to identify *BRCA1/2* gene variants would occur at diagnosis of mCRPC, with olaparib used as a second- or later-line treatment option (i.e. patients with a pathogenic *BRCA1/2* variant who received NHA in first-line would be eligible for olaparib in second-line, and patients who received docetaxel in first-line and NHA in second-line would be eligible for olaparib in third-line). The proposed clinical management algorithm in the submission did not include the flow on to germline and cascade testing and explicitly depict that tumour testing leads to germline testing (after counselling, if tumour testing is positive), followed by cascade testing (after counselling, if germline testing is positive).
- 4.3 The ESCs noted that the clinical management algorithm of mCRPC patients is changing. For example, both apalutamide and darolutamide, which are also NHAs, have been considered by the PBAC for use in non-metastatic CRPC. If recommended, it is probable that NHA use in the non-metastatic CRPC setting would prohibit NHA use in the mCRPC setting. Therefore, for patients with *BRCA1/2* pathogenic gene variants, olaparib would become first-line treatment in mCRPC in patients who have predicted

intolerance to docetaxel and second-line treatment in patients who have failed treatment with docetaxel.

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

5 Comparator

- 5.1 The main comparator for testing of tumour tissue to detect *BRCA1/2* gene variants in patients with mCRPC is no genetic testing. The ratified PICO for Application 1618 stated that PASC confirmed the comparator for the test.
- 5.2 The submission nominated physician's choice of NHA (abiraterone or enzalutamide) as the main comparator for olaparib. The ESCs noted that the nominated comparator does not reflect current Australian practice and ignores the PBS listing criteria for both abiraterone and enzalutamide which expressly prevent sequential use of NHAs. The PBAC has previously considered the issue of sequential use of NHA and considered it unlikely subsequent NHA would demonstrate efficacy following progression on a prior NHA due to pharmacological similarity. The PBAC previously noted evidence from a phase IV trial in 251 patients who had previously responded to enzalutamide and then progressed (Attard 2017¹) which indicated that abiraterone has only minimal activity in patients who progressed after treatment with enzalutamide. For enzalutamide following abiraterone, a single-arm Phase IV study² showed that enzalutamide had some anti-tumour activity, following progression on abiraterone, although many patients had developed cross-resistance. On this basis, the PBAC has previously also recommended that use of abiraterone and enzalutamide in the metastatic setting following apalutamide and darolutamide in the non-metastatic setting would not be appropriate due to the potential for cross-resistance, uncertainty regarding the magnitude of benefit and uncertain cost effectiveness (see paras 2.7, 4.7, 6.46, 7.4, 7.13 apalutamide November 2018, 2.5, 2.6, 7.3 and 7.4 apalutamide July 2019 and paras 3.1, 7.4 darolutamide July 2020 Public Summary Document (PSD)). The Pre-Sub-Committee Response (PSCR) stated that, despite the PBS restrictions, a 2016 DUSC analysis found that large number of patients (24%) received abiraterone or enzalutamide without the use of prior docetaxel and that some patients (11%) received sequential use of NHAs. The ESCs noted that the 2016 DUSC analysis stated that in the trials approximately 5% of patients developed intolerance to an NHA and needed to be switched and that DUSC therefore considered that a proportion of the

¹ Attard G, Borre M, Gurney H, et al. A phase IV, randomized, double-blind, placebo-controlled study of continued enzalutamide post prostate-specific antigen progression in men with chemotherapy-naïve metastatic castration-resistant prostate cancer (abstract 5004). 2017 American Society of Clinical Oncology meeting.

² de Bono JS, Chowdhury S, Feyerabend S, et al. Antitumour Activity and Safety of Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer Previously Treated with Abiraterone Acetate Plus Prednisone for ≥24 weeks in Europe. *Eur Urol* 2018; 74:37.

11% of patients who transitioned between NHAs was legitimate use after patients developed intolerance.³ The PSCR also stated that a recent analysis of a Medicare 10% PBS sample found that in 2019, 79% of patients received an NHA as a first-line treatment in mCRPC and that NHAs were prescribed sequentially in 49% of patients. The ESCs noted that the sponsor's data could not be verified and that updated data provided by DUSC (Jan-Jun 2018 with follow up to December 2019, see Table 2) indicated that 52% of patients received an NHA as a first-line treatment in mCRPC and that 9% of patients receiving a second treatment received sequential NHA. The ESCs considered that a large proportion of the 9% sequential use would be switching due to intolerance, rather than subsequent treatment following progression. The ESCs also noted that only 35% of patients go on to receive second-line treatment for mCRPC (254/729 = 35%) and following prior NHA therapy 71% of patients did not have a subsequent treatment within 18-24 months of follow up.

Table 2: DUSC 2019 analysis of scripts for mCRPC (6 month first initiating cohort (Jan-Jun 2018 with follow up to December 2019))

	First line mCRPC n/N (%)	Second line mCRPC n/N (%) ^a	Following prior NHA n/N (%) ^b
Docetaxel	337/729 (46.2)	57/254 (22.4)	57/418 (13.6)
NHA (abi or enza)	377/729 (51.7)	172/254 (67.7)	24/418 (5.7)
Other	15/729 (2.1)	NA	NA
Cabazitaxel		25/254 (9.8)	41/418 (9.8)
No treatment	NA	NA	296/418 (70.8)
Sequential NHA	-	24/254 (9.4)	-

^a Denominator is count of patients with a subsequent therapy

^b Denominator is count of patients with first line NHA, or second line NHA and a subsequent therapy

5.3 Based on the DUSC data in Table 2, the ESCs considered that a mixed comparator might be appropriate: best supportive care (BSC): 75%, docetaxel: 15%, cabazitaxel: 10%. Sequential use of NHAs due to toxicity would not be a comparator because this would still be considered initial (first-line) NHA use. The pre-PBAC response cited the 2019 10% PBS data sample, stating that of patients who received sequential NHA, 20% were sequenced NHA treatments on progression (based on having 4 or more scripts of their initial NHA). The sponsor proposed that a more appropriate mixed comparator would consist of: NHA, 20%; BSC, 55%; docetaxel, 15%; and cabazitaxel, 10%. The PBAC, noting the issues with sequential NHA use, considered that BSC or cabazitaxel, (which is currently PBS listed for use following docetaxel), would be appropriate comparators.

³ DUSC. Metastatic prostate cancer: predicted versus actual analysis. June 2016. Available at: <https://www.pbs.gov.au/industry/listing/participants/public-release-docs/2016-06/prostate-cancer-DUSC-PRD-June-2016-final.pdf>

- 5.4 The ESCs acknowledged that as there are no head-to-head trials comparing olaparib with BSC, cabazitaxel or docetaxel, any comparison would be an indirect treatment comparison. However, an indirect treatment comparison from the *BRCA*+ subgroup of olaparib arm of PROfound to all-comers trials with BSC or docetaxel or cabazitaxel as treatment arms would be subject to transitivity problems leading to bias. Therefore, in view of the expected poor efficacy of any of the alternative therapies for the requested population, the comparative results of the PROfound trial may represent reasonable estimates of the effectiveness of olaparib over a mixed comparator (BSC, docetaxel, cabazitaxel). Even this pragmatic option would tend to overestimate the incremental advantage to olaparib because medicines from another class of medicines (such as cabazitaxel and docetaxel) are more likely to have an effect than the second sequential NHA which would likely have minimal activity due to cross resistance.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of prostate cancer and the medications currently available for the treatment of mCRPC and the changes in the clinical algorithm with NHAs being used earlier in the treatment algorithm. The clinician noted the unmet need for novel treatments that do not target the hormone receptor, given the potential for cross-resistance between NHAs and also between NHAs and taxanes. The clinician also discussed the incidence of *BRCA1/2* gene variants, which varies in the literature depending on how enriched the cohorts are for advanced and aggressive cancers. The clinician considered the incidence from the screening component of the PROfound trial provided the best basis for estimating the incidence of *BRCA1/2* gene variants.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from two organisations via the Consumer Comments facility on the PBS website. No comments on this submission were received from individuals.
- 6.3 The PBAC noted the advice received from the Prostate Cancer Foundation of Australia confirming its support for the olaparib submission. The PBAC specifically noted the advice that the use of olaparib has the potential to improve the quality of life of patients with prostate cancer. The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the olaparib submission. 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 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement), based on a comparison with abiraterone or enzalutamide.⁴

Clinical trials

- 6.5 The approach taken in the submission was to present evidence that has been linked to support the contention that targeting of patients with *BRCA1/2* pathogenic variants (either somatic or germline) with olaparib will result in improved clinical outcomes in patients mCRPC who failed NHA treatment.

Table 3: Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied
Accuracy and performance of the test (analytical validity)	The submission did not conduct a search for studies of diagnostic performance. The following data was included for: F1CDx: the summary of two concordance analyses included in the FDA label comparing F1CDx with evNGS and F1LTD. QIAseq: A validation report conducted by the PMCC comparing QIAseq to two in-house NGS assays: CCP and the FRCP.	☐ k=0
Prognostic evidence	Comparison of outcomes in patients receiving usual care conditioned on the presence or absence of biomarker positive status.	☒ k=2 n=13,369
Clinical utility of the test	The submission did not compare outcomes in patients with and without <i>BRCA1/2</i> pathogenic variants who received olaparib or NHA. This information is available from the PROfound trial, with patients without <i>BRCA1/2</i> pathogenic variants forming the complement.	☐ k=0
Change in patient management	No evidence was provided to show that biomarker determination guides decisions about treatment with the medicine.	☐ k=0
Treatment effectiveness	PROfound trial: open label, randomised, phase 3 study of olaparib versus enzalutamide or abiraterone in mCRPC with HRR alterations and a subpopulation with <i>BRCA1/2</i> pathogenic gene variants.	☒ k=1 n=245

Source: Constructed during the evaluation.

BRCA1/2 = breast cancer genes 1 and 2; CCP = Comprehensive Cancer Capture Panel; evNGS = externally validated NGS assay; F1CDx = FoundationOne®CDx; F1LTD = FoundationOne laboratory developed test; FRCP = Familial Risk Cancer Panel; HRR = homologous recombination repair; k = number of studies; mCRPC = metastatic castration resistant prostate cancer; n = number of patients; NGS = next generation sequencing; NHA = novel hormonal agent.

⁴ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017]

6.6 The following table outlines the data that were available to address the comparisons.

Table 4: Summary of the linked evidence approach

Proposed test versus no test	No evidence presented	
Proposed test versus alternative test	No evidence presented	
	Olaparib	NHA
Biomarker test positive	PROfound	PROfound
Biomarker test negative	No evidence presented	No evidence presented

Source: Compiled during the evaluation.

NHA = novel hormonal agent.

- 6.7 In regard to the open-label design of the PROfound trial, the submission stated that blinded independent central review (BICR) of all scans was used to ensure the robustness of the primary endpoint, which was assessment with analysis of radiological progression-free survival (rPFS). As such the risk of bias with the PROfound trial can be considered low in regard to outcome assessment.
- 6.8 The submission did not consider the potential for bias relating to the use of subgroup results for the key outcomes. The CSR noted that PROfound was not powered to assess efficacy within individual subgroups and due to the multiple testing, the subgroup analyses should be interpreted with caution.
- 6.9 There is also potential for bias given that patients in the comparator arm of PROfound were receiving sequential NHA treatments. This could potentially favour olaparib, as treatment in the comparator arm is likely to be an inferior treatment option compared with clinical practice, due to the potential for cross-resistance with sequential NHA treatments.

6.10 Details of the trial presented in the submission are provided in the tables below.

Table 5: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
PROfound	A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have Homologous Recombination Repair Gene Mutations (PROfound). de Bono J, Mateo J, Fizazi K et al. Olaparib for metastatic castration-resistant prostate cancer. de Bono J, Hussain M, Thiery-Vuillemin A et al. PROfound: a randomized phase III trial evaluating olaparib in patients with metastatic castration-resistant prostate cancer and a deleterious homologous recombination DNA repair aberration ^a . Sandhu SK, Hussain M et al. PROfound: Phase III study of olaparib versus enzalutamide or abiraterone for metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations.	October 2019 NEJM 2020; 382(22): 2091-2102 J Clin Oncol 2018; 35(15 suppl): abstract TPS5091 ^a Ann Oncol 2019; 30(suppl 5): v851-v934
PROfound final analysis	A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have Homologous Recombination Repair Gene Mutations (PROfound). Final Analysis of Overall Survival and Safety Update. Hussain M, Mateo J, Fizazi K et al. Survival with olaparib in metastatic castration-resistant prostate cancer. NEJM 2020. (Online ahead of print).	July 2020 NEJM 2020. DOI: 10.1056/NEJMoa2022485

Source: Table 2-3, p64 of the submission.

^a The submission provided an incorrect journal source for this abstract (Oncology Research and Treatment), and the correct source has been provided. The submission also cited another abstract by Feyerabend S et al (2020), also in Oncology Research and Treatment, but this article could not be sourced, nor could any relevant article by the named author be identified. The submission did not provide either abstract.

Table 6: Key features of the included evidence

Trial	N	Design	Patient population	Key outcomes reported in the submission	Use in modelled evaluation
Olaparib vs. NHA					
PROfound Cohort A+B	386	R, OL, MC	BRCA1/2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L pathogenic gene variants	Safety	Selected safety outcomes
PROfound Cohort A (ITT)	245	R, OL, MC	BRCA1/2, ATM pathogenic gene variants	rPFS*, OS, safety	EQ-5D-5L outcomes
PROfound BRCA1/2 subgroup	160 [^]	R, OL, MC	BRCA1/2 pathogenic gene variants	rPFS, OS	rPFS, OS (extrapolated)

Source: Table 2.4, p66 of the submission.

ITT = intention to treat population; MC = multicentre; OL = open label; OS = overall survival; R = randomised; rPFS = radiological progression-free survival.

* trial primary outcome, note other predefined alpha controlled secondary outcomes in trial include: confirmed overall response rate (ORR) in Cohort A, rPFS (BICR) Cohorts A+B, time to pain progression in Cohort A and OS in Cohort A, interim and final.

[^] Also includes 1 patient in each arm from Cohort B.

- 6.11 The PROfound trial was split into two cohorts, Cohort A which included patients with *BRCA1/2* or *ATM* pathogenic variants, and Cohort B which included patients with one or more pathogenic variants in the other 12 genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*). Cohort B also erroneously enrolled two patients with *BRCA1/2* pathogenic variants, these patients were included in all *BRCA1/2* subgroup analyses. The primary and key secondary outcomes of the trial were assessed for Cohort A (the ITT population). rPFS and overall survival (OS) results for the *BRCA1/2* pathogenic gene variant population (a subgroup of Cohort A and Cohort B) were also reported. Safety outcomes were based on the combined Cohort A and Cohort B.
- 6.12 While the submission provided results for the *BRCA1/2* subgroup for OS and rPFS outcomes, the submission did not provide baseline demographic and disease characteristic information for the *BRCA1/2* subgroup and its complement (as recommended in the PBAC Guidelines, p34). The subgroup results provided were also limited, with no results provided for the subgroup complement, or for the test for interaction of effectiveness. The ESCs noted that patient demographics and baseline characteristics (provided with the PSCR) were broadly similar between the two arms of the *BRCA1/2* subgroup and to the whole of the Cohort A population.
- 6.13 The PSCR stated that there is a clear lack of benefit in non-*BRCA1/2* subgroups. The HR for the secondary endpoint of PFS for the post hoc defined *BRCA1/2* positive subgroup in Cohort A of PROfound was 0.22 (95% CI: 0.15, 0.32); median duration: 10 months versus 3 months. The HR for PFS for the complement *ATM* positive subgroup was 1.04 (95% CI: 0.61, 1.87), with a test for interaction across the subgroups yielding a p-value of <0.0001. The PBAC considered this was a reasonable basis on which to accept the *BRCA1/2* subgroup results over the ITT results from Cohort A of PROfound.

Comparative effectiveness

6.14 Key time-to-event outcomes from PROfound are summarised in the table below.

Table 7: Summary of rPFS and OS reported in PROfound

	Number of events/total number of patients (%)		HR (95% CI)	Median duration (95% CI), months	
	Olaparib	NHA	HR	Olaparib	NHA
Radiological progression-free survival (rPFS) – BICR assessed (data cut off: 4 June 2019)					
Cohort A (ITT) ^a (BRCA1/2, ATM)	106/162 (65.4)	68/83 (81.9)	0.34 (0.25, 0.47)	7.39 (6.24, 9.33)	3.55 (1.91, 3.71)
Cohort A+B	180/256 (70.3)	99/131 (75.6)	0.49 (0.38, 0.63)	5.82 (5.52, 7.36)	3.52 (2.20, 3.65)
Cohort A + B (BRCA1/2)	62/102 (60.8)	51/58 (87.9)	0.22 (0.15, 0.32)	9.79 (7.62, 11.30 ^a)	2.96 (1.81, 3.55)
Cohort A + B (BRCA1/2, ATM) ^b	108/165 (65.5)	69/84 (82.1)	0.38 (0.28, 0.52)	7.39 (6.87, 9.33)	3.52 (1.87, 3.65)
Cohort B genes ^c	30/39 (76.9)	16/24 (66.7)	1.00 (0.55, 1.88)	3.91 (2.00, 7.20)	3.71 (1.87, 5.75)
Any single HRR gene ^d	169/239 (70.7)	91/120 (75.8)	0.53 (0.41, 0.69)	6.08 (5.52, 7.36)	3.52 (1.97, 3.71)
BRCA1 ^d	7/8 (87.5)	5/5 (100)	0.41 (0.13, 1.39)	2.07 (1.38, 5.52)	1.84 (1.71, 3.71)
BRCA2 ^d	47/81 (58.0)	40/47 (85.1)	0.21 (0.13, 0.32)	10.84 (9.17, 13.08)	3.48 (1.74, 3.65)
ATM ^d	46/62 (74.2)	17/24 (70.8)	1.04 (0.61, 1.87)	5.36 (3.61, 6.21)	4.70 (1.84, 7.26)
CDK12 ^d	47/61 (77.0)	18/28 (64.3)	0.74 (0.44, 1.31)	5.09 (3.61, 5.52)	2.20 (1.71, 4.83)
Overall survival (OS) (final analysis, data cut off 20 March 2020)					
Cohort A (ITT) ^a (BRCA1/2, ATM)	91/162 (56.2)	57/83 (68.7)	0.69 (0.50, 0.97)	19.09 (17.35, 23.43)	14.69 (11.93, 18.79)
-Adjusted ^f for 67% crossed over	-	-		-	11.73 (NR, NR)
Cohort A+B	160/256 (62.5)	88/131 (67.2)	0.79 (0.61, 1.03)	17.31 (15.47, 18.63)	14.00 (11.47, 17.08)
Cohort A + B (BRCA1/2)	53/102 (52.0) ^e	41/58 (70.7) ^e	0.63 (0.42, 0.95)	20.11 (17.35, 26.81)	14.44 (10.71, 18.89)
Cohort A + B (BRCA1/2, ATM) ^b	93/165 (56.4)	58/84 (69.0)	0.70 (0.51, 0.98)	19.09 (17.35, 23.43)	14.62 (11.93, 18.79)
Non-BRCA pathogenic variants	107/154 (69.5)	47/73 (64.4)	0.95 (0.68, 1.34)	15.80 (13.86, 17.31)	13.34 (11.17, 17.74)
Cohort B genes ^c	69/94 (73.4)	31/48 (64.6)	0.96 (0.63, 1.49)	14.1 (11.1, 15.9)	11.5 (8.2, 17.1)
-Adjusted ^f for 63% crossed over	-	-	0.83 (0.11, 5.98)	-	-
Any single HRR gene	NR	NR	NR	NR	NR
BRCA1 ^d	5/8 (62.5)	5/5 (100)	0.42 (0.12, 1.53)	11.70 (1.38, NC)	9.40 (5.45, 14.62)
BRCA2 ^d	39/81 (48.1)	32/47 (68.1)	0.59 (0.37, 0.95)	24.84 (17.35, NC)	15.15 (10.71, 19.75)
ATM ^d	39/62 (62.9)	15/24 (62.5)	0.93 (0.53, 1.75)	18 (14.42, 23.43)	15.57 (12.12, 22.01)
-Adjusted ^f for 63% crossed over	-	-	0.84 (0.19, 3.75)	-	-
CDK12 ^d	47/61 (77.0)	18/28 (64.3)	0.97 (0.57, 1.71)	14.06 (11.14, 15.87)	11.47 (7.82, 17.74)

Bold = statistically significant

Source: TGA delegate overview (Table 5), PROfound CSR sections tables listings figures.pdf (Table 14.2.1.4.1, 14.2.5.1.). Hussain et al 2020 publication and supplement. Table 2-13, p85; Table 2-30, p94; Section 2.2.D.7, p113-125 of the submission.

BICR = blinded independent central review; BRCA = breast cancer gene; CI = confidence interval; HR = hazard ratio; HRR = homologous recombination repair; ITT = intention to treat; NC = not calculable; NHA = novel hormonal agent (abiraterone, enzalutamide); NR = not reported; OS = overall survival; rPFS = radiological progression-free survival.

^a primary end point

^a note this was incorrectly reported in the submission as 11.20

^b patients with single and co-mutations

^c includes patients with the following mutations from PROfound: BARD1 &/or BRIP1 &/or CHEK1 &/or CHEK2 &/or PALB2 &/or PPP2R2A &/or RAD51B &/or RAD51D

^d gene subgroup analysis is based on patients with a single HRR mutation (results presented for genes with >10 patients in each arm in the trial)

^e the number and proportion of deaths in the BRCA1/2 subgroup was not provided by the submission, but was available in Table 14.2.4.5 of the CSR addendum supplementary tables provided with the submission

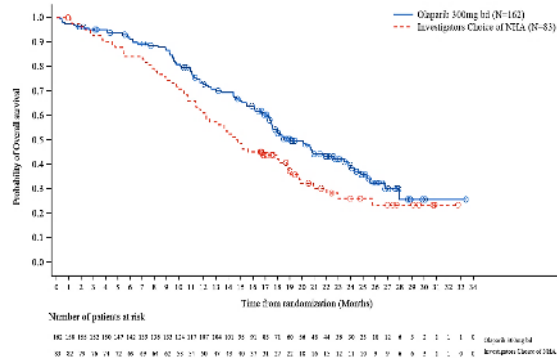
^f rank preserving structural failure time model (RPSFTM) used to adjust for patient who crossed over from NHA to olaparib treatment.

¹ Adjusted OS hazard ratio: manuscript submitted to European Urology for publication.

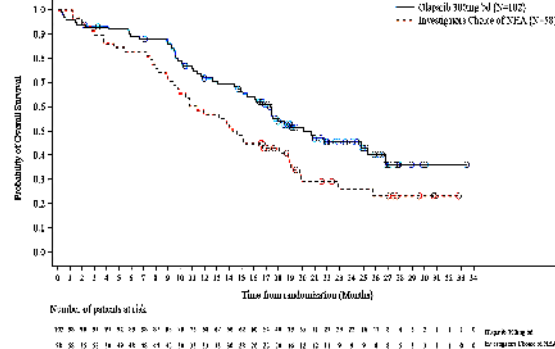
- 6.15 For the primary outcome of rPFS assessed by BICR in Cohort A patients, there was a statistically significant advantage for olaparib compared to NHA (HR = 0.34; 95% CI: 0.25, 0.47). For investigator-assessed rPFS, the hazard ratio lowered, indicating a greater advantage for olaparib, although the submission noted that the open label nature of the trial should be considered a factor in the results. The advantage observed for the BICR assessed *BRCA1/2* subgroup was numerically greater than that observed in Cohort A (HR = 0.22; 95% CI: 0.15, 0.32). A similar benefit in rPFS for olaparib versus NHA was not shown in the complement subgroups: *ATM* (HR = 1.04; 95% CI: 0.61, 1.87), *CDK12* (HR = 0.74; 95% CI: 0.44, 1.31) or Cohort B genes (HR = 1.00; 95% CI: 0.55, 1.88). However, as PROfound was not alpha corrected to assess efficacy within individual subgroups these results should be interpreted with caution.
- 6.16 The final analysis of OS in Cohort A demonstrated a statistically significant advantage for olaparib, indicating a 4.4 month gain in survival for olaparib-treated patients (HR = 0.69; 95% CI: 0.50, 0.97). The analysis in the *BRCA1/2* subgroup showed an incremental gain in survival of 5.7 months (HR = 0.63; 95% CI: 0.42, 0.95). The Kaplan Meier plots for OS for Cohort A and *BRCA1/2* subgroup are provided below. At the March 2020 data cut, the median duration of follow up was 21.91 months for the olaparib arm and 21.04 months for the NHA arm. A similar benefit in OS for olaparib versus NHA was not shown in the complement subgroups: *non-BRCA* (HR = 0.95; 95% CI: 0.68, 1.34), *ATM* (HR = 0.93; 95% CI: 0.53, 1.75), *CDK12* (HR = 0.97; 95% CI: 0.57, 1.71) or Cohort B genes (HR = 0.96; 95% CI: 0.63, 1.49), available Kaplan Meier graphs for Cohort B and *ATM* subgroup are also presented below and show no separation in the OS curves between those treated with olaparib and NHA.

Figure 1: Kaplan Meier plot of OS for the PROfound trial – final analysis (March 2020 data cut)

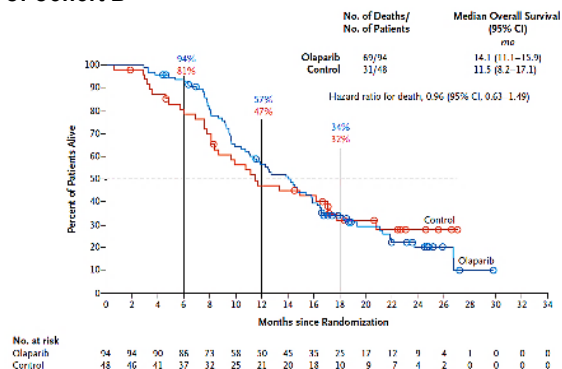
A: Cohort A



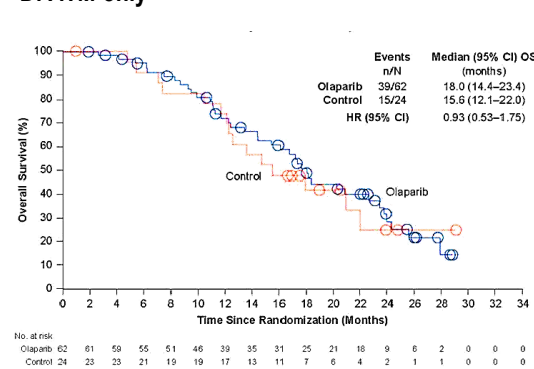
B: BRCA1/2 subgroup^a



C: Cohort B



D: ATM only



Source: Figure S1, p16 of the CSR addendum^a; Figure 2-9, p115 of the submission, C and D were not presented in the submission and were extracted from Hussain et al 2020 (publication and supplement) during the evaluation.

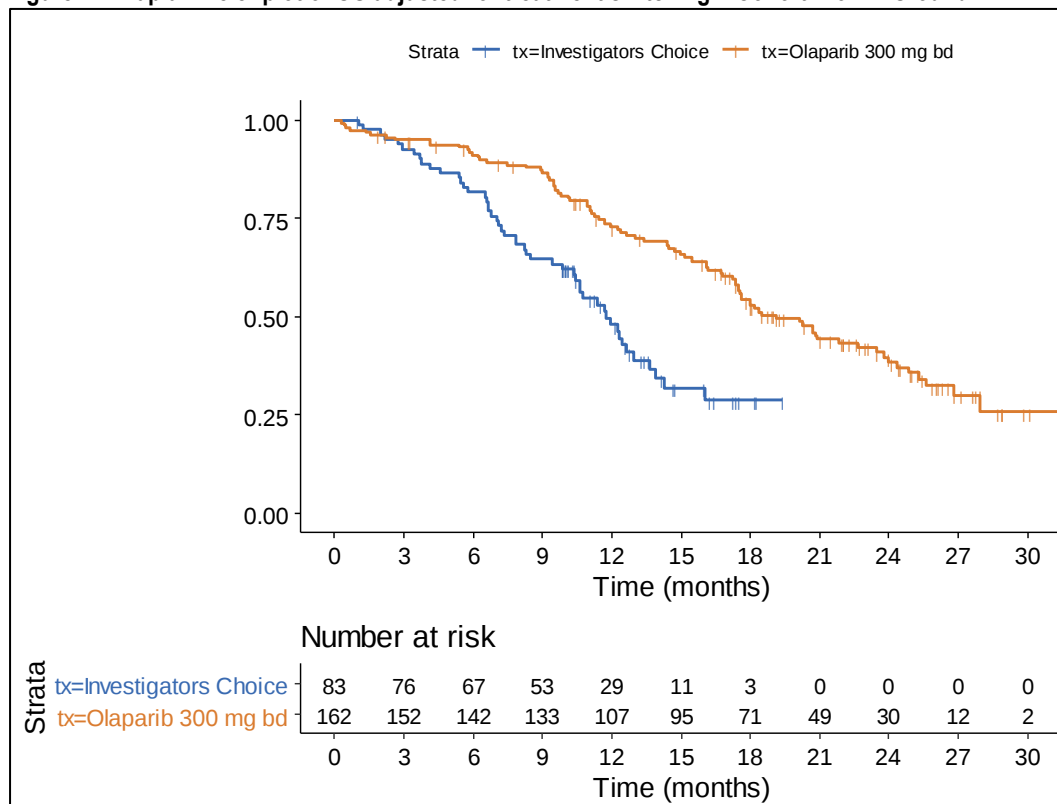
NHA = novel hormonal agent (abiraterone; enzalutamide); OS = overall survival.

^a The submission provided Figure 2.7, p94 as the Kaplan Meier plot for OS, however that plot appeared to have the months along the x axis to only 25 months, and patient numbers and months did not correspond to number of patients at risk, so the source plot from the CSR addendum has been provided.

6.17 The submission stated that 67.5% of NHA-treated patients (N=56) had received subsequent treatment with olaparib, and that the effect of treatment switching on OS was addressed through the use of the rank preserving structural failure time model (RPSFTM). As indicated in the table above, the resultant adjusted HR in Cohort A was [REDACTED]⁵, which was further from the null value of 1.0 than the unadjusted result (HR = 0.69; 95% CI: 0.50, 0.97). The adjusted Kaplan Meier plot is provided below.

⁵ Adjusted OS hazard ratio: manuscript submitted to European Urology for publication.

Figure 2: Kaplan Meier plot of OS adjusted for treatment switching – Cohort A of PROfound



Source: Figure 2-19, p123 of the submission.

bd = twice daily; NHA = novel hormonal agent (abiraterone; enzalutamide); OS = overall survival; tx = treatment.

- 6.18 While it is appropriate to adjust for treatment switching, the ESCs noted that the submission did not provide results for other methods of adjustment, as recommended by the PBAC Guidelines. The RPSFTM may not have been the most appropriate method to use as it makes the assumption of a common treatment effect. The PSCR stated that RPSFTM is not restricted in its application to trials in which the comparator arm receives a non-active comparator, noting that the RPSFTM methodology was utilised in a recent publication⁶. The ESCs considered that PROfound may not meet the common treatment effect assumption that underlies RPSFTM analyses. The PSCR stated that the common treatment effect assumption was difficult to assess, but noted that a sensitivity analysis in which a proportion of the olaparib treatment effect was applied to those switching to olaparib demonstrated that if the treatment effect were to decrease post-progression, it would still result in an overall benefit for patients who switched.

⁶ de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic-castration-resistant prostate cancer. NEJM. 2020;382:2091-2102.

6.19 The submission stated that OS results for the *BRCA1/2* subgroup, adjusted for treatment switching, were applied in the economic model. Further data were provided in the PSCR demonstrating that the *BRCA1/2* subgroup was adjusted for treatment switching using the RPSFTM method (Cox proportional hazards model with recensoring) – see table below. This resulted in a HR of [REDACTED]⁷ for OS in the *BRCA1/2* subgroup. This value was lower than the unadjusted HR for OS in the *BRCA1/2* subgroup population of 0.63 (95% CI: 0.42, 0.95). Without recensoring the OS HR for the *BRCA1/2* subgroup, using the RPSFTM method (Cox proportional hazards model), increased to [REDACTED]⁷. The Guidelines for preparing submissions to PBAC state that methods for adjusting the treatment effect for treatment switching may rely on assumptions that are difficult to validate. Consequently, it is preferable to use a number of different statistical approaches to adjust for switching. Similar results will reduce uncertainty and increase confidence in the treatment effect used in the economic model. In this case, two statistical approaches were used (RPSFT models with and without reensoring) and the results were materially different, increasing uncertainty.

Table 8: Results for RPSFTM adjusted OS for Cohort A and the *BRCA1/2* subgroup

	Cohort A		BRCA1/2 subgroup	
	Olaparib (N = 162)	NHA (N = 83)	Olaparib (N = 102)	NHA (N = 58)
Overall survival (OS) (final analysis, data cut off 20 March 2020)				
Deaths, n (%)	91 (52.6%)	57 (65.7%)	53 (52.0%) ^a	41 (70.7%) ^a
Median, months (95% CI)	19.09 (17.35, 23.43)	14.69 (11.93, 18.79)	20.11 (17.35, 26.81)	14.44 (10.71, 18.89)
HR (95% CI)	0.69 (0.50, 0.97)		0.63 (0.43, 0.95)	
Overall survival (OS) adjusted for crossover using RPSFTM – with recensoring (final analysis, data cut off 20 March 2020)				
Deaths, n (%)	NR	NR	NR	NR
Median, months (95% CI)	NR	11.73	NR ^b	9.15
HR (95% CI)	[REDACTED] ¹		[REDACTED] ¹	
Overall survival (OS) adjusted for crossover using RPSFTM – without recensoring (final analysis, data cut off 20 March 2020)				
Deaths, n (%)	NR	NR	NR	NR
Median, months (95% CI)	NR	11.99	NR ^b	9.57
HR (95% CI)	0.50 (0.27, 0.93)		[REDACTED] ¹	

Source: p6-7 of Attachment 1 of the PSCR; Table 4.4, p10 of the PSCR.

BRCA1/2 = breast cancer genes 1 and 2; CI = confidence interval; HR = hazard ratio; NHA = novel hormonal agent; NR = not reported; OS = overall survival; RPSFTM = rank preserving structural failure time model.

^a the number and proportion of deaths in the *BRCA1/2* subgroup was not provided by the submission, but was available in Table 14.2.4.5 of the CSR addendum supplementary tables provided with the submission.

^b the PSCR provided the median months of survival for the NHA group (9.15 with recensoring and 9.57 without) and the difference between olaparib and NHA arms (11.0 months with recensoring and 10.5 without), thus the median OS in the olaparib arm can be calculated to be 20.15 months with recensoring and 20.07 without recensoring.

¹ Adjusted OS hazard ratio: manuscript submitted to European Urology for publication.

⁷ Adjusted OS hazard ratio: manuscript submitted to European Urology for publication.

- 6.20 The ESCs noted that the submission did not consider the olaparib-treated patients who moved to an alternate therapy following progression. Almost half (48.8%) of olaparib-treated patients received subsequent treatment, with 17.3% of patients switching to an NHA. In the Australian context such a treatment sequence would not be permitted, as NHAs cannot be used sequentially. The ESCs considered that, given the relatively small proportion of olaparib patients subsequently receiving an NHA, not adjusting for this presented a low risk of bias in the overall adjustment for treatment switching.
- 6.21 Overall, the ESCs considered the treatment switching observed in the PROfound trial has not been appropriately adjusted for, and the presented results (and as applied in the economic model) were not likely to accurately reflect OS in the proposed PBS population.

Comparative harms

- 6.22 The safety data presented in the submission was based on Cohort A + B of the PROfound trial. Thus, along with the 245 patients in Cohort A, an additional 141 patients in Cohort B (those with 12 other gene variants) were included. Safety results for the proposed PBS population, patients with *BRCA1/2* pathogenic gene variants, were not separately available.
- 6.23 The following table provides a summary of treatment-related AEs in Cohort A + B of PROfound.

Table 9: Summary of key adverse events Cohort A and Cohort B of PROfound

AEs causally related to trial treatment	Olaparib (N=256) n (%)	NHA (N=130) n (%)	RD (95% CI)^
Any AE	210 (82.0%)	63 (48.5%)	0.34 (0.24, 0.43)
AE ≥ Grade 3	83 (32.4%)	12 (9.2%)	0.23 (0.16, 0.31)
AE with outcome=death	1 (0.4%)	1 (0.8%)	-0.003 (-0.02, 0.01)
SAE (including events with outcome=death)	36 (14.1%)	6 (4.6%)	0.09 (0.04, 0.15)
AE leading to discontinuation	35 (13.7%)	6 (4.6%)	0.09 (0.04, 0.15)
AE leading to dose reduction	52 (20.3%)	6 (4.6%)	0.16 (0.10, 0.22)
AE leading to dose interruption	90 (35.2%)	11 (8.5%)	0.27 (0.19, 0.34)

Source: Table 2-32, p100 of the submission.

AE = adverse event; NHA = novel hormonal agent; RD = risk difference; SAE = serious adverse event.

^ Estimated during the evaluation using STATA 14.

- 6.24 Significantly greater proportions of patients treated with olaparib experienced any AE, AE ≥ Grade 3, serious AE, AE leading to discontinuation, AE leading to dose reduction and AE leading to dose interruption in Cohort A + B. However, there was no difference in AEs that resulted in death between the two treatment arms.
- 6.25 The submission stated that the safety and tolerability profile of olaparib in PROfound was consistent with the known safety and tolerability profile of olaparib and considered to be mostly manageable and acceptable in this population. This was

reasonable for some AEs, such as the occurrence of anaemia associated with olaparib, which had been cited as a relevant AE in the November 2019 consideration of olaparib (paragraph 7.15, November 2019 PSD).

- 6.26 The PBAC noted that the EMA stated that uncertainties remain regarding the potential risks of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), new primary malignancies and pneumonitis, which require monitoring in the post-marketing setting. The PSCR stated that while the events of MDS/AML and pneumonitis are being monitored, no MDS/AML cases were noted in the PROfound trial. The PSCR stated that a low occurrence of pneumonitis was observed in both the olaparib (2.0%) and NHA (1.5%) arms of the trial.
- 6.27 Overall, the ESCs also noted that these risks were previously considered acceptable for patients with ovarian cancer. The economic model included AEs such as anaemia, neutropenia, pulmonary embolism and vomiting, along with skeletal-related events which were not included in the submission's discussion of the safety of olaparib.

Benefits and harms

- 6.28 A summary of the comparative benefits and harms for olaparib versus NHA is presented in the table below.

Table 10: Summary of comparative benefits and harms for olaparib and NHA

Benefits – PROfound						
rPFS – Cohort A ITT	Olaparib N=102	NHA N=58	Absolute difference	HR (95% CI)		
Progression event, n (%)	NR	NR	-	0.34 (0.25, 0.47)		
% progression-free (95% CI)	NR	NR	-			
Median months to rPFS (95% CI)	9.79 (7.62, 11.20)	2.96 (1.81, 3.55)	6.83			
% progression-free at 6 mths (95% CI)	NR	NR	-			
% progression-free at 12 mths (95% CI)	NR	NR	-			
Overall survival – Cohort A ITT						
Died, n (%)	91 (56.2%)	57 (68.3%)	-	0.69 (0.50, 0.97)		
% alive (95% CI)	43.8% (NR)	31.7% (NR)	12.1			
Median months to death (95% CI)	19.09 (17.35, 23.43)	14.69 (11.93, 18.79)	4.4			
% alive at 6 mths (95% CI)	NR	NR	-			
% alive at 12 mths (95% CI)	NR	NR	-			
Harms – PROfound						
Cohort A+B	Olaparib N=256	NHA N=130	RR (95% CI)	Events/100 patients		RD (95% CI)
				Olaparib	NHA	
Anaemia	52 (22.7%)	7 (5.4%)	NR	23	5	NR
Neutropenia	10 (3.9%)	0 (0. 0%)	NR	4	0	NR
Pneumonia	8 (3.1%)	3 (2.3%)	NR	3	2	NR

Source: Compiled during the evaluation.

CI = confidence interval; HR = hazard ratio; mths = months; NHA = novel hormonal agent; NR = not reported; RD = risk difference; rPFS = radiological progression-free survival; RR = relative risk.

- 6.29 On the basis of the evidence presented by the submission for the *BRCA1/2* subgroup, no statements regarding the number of patients progression-free or number of patients alive when treated with olaparib compared to NHA can be made, given the required data was not provided by the submission.
- 6.30 In regard to harms, for every 100 patients treated with olaparib, approximately 18 additional patients would experience anaemia, 4 additional patients would experience neutropenia and 1 additional patient would experience pneumonia over 277 days of treatment.

Clinical claim

- 6.31 The submission claimed that olaparib has superior efficacy and an increased but manageable toxicity burden compared to currently listed NHA treatments for the treatment of *BRCA1/2* positive mCRPC. The ESCs considered that while the evidence demonstrated statistically significant advantages for olaparib compared to the NHAs of abiraterone and enzalutamide, there remained a number of concerns, including:
- The nominated comparator of NHAs does not reflect current Australian practice and ignores the PBS listing criteria for both abiraterone and enzalutamide, which expressly prevent sequential use of NHAs. The PBAC has previously considered it unlikely subsequent NHA would demonstrate efficacy following progression on a prior NHA due to pharmacological similarity. As such, the ESCs considered that the results of PROfound were likely to be biased in favour of olaparib.
 - The key trial results were based on the *BRCA1/2* subgroup from PROfound, which corresponded to the proposed PBS population. The Commentary considered that the submission did not provide adequate information to determine the reliability of the subgroup evidence, however the ESCs considered that further information provided in the PSCR helped support reliance on the results for the *BRCA1/2* subgroup over those for the ITT population of Cohort A.
 - The OS results for the *BRCA1/2* subgroup were adjusted for treatment switching using the RPSFTM method (Cox proportional hazards model with recensoring). This resulted in an adjusted hazard ratio of [REDACTED]⁸ for OS in the *BRCA1/2* subgroup, which was significantly lower than the unadjusted hazard ratio in the *BRCA1/2* subgroup population (HR = 0.69; 95% CI: 0.50, 0.97). The sponsor presented two statistical approaches to adjust for switching (RPSFT models with and without recensoring). The results were materially different, increasing uncertainty about the treatment effect for OS in the proposed PBS population.

⁸ Adjusted OS hazard ratio: manuscript submitted to *European Urology* for publication.

- 6.32 The PBAC considered that the use of NHA as the comparator was not appropriate, but that olaparib demonstrated clinical efficacy in the *BRCA1/2* subgroup and a claim of superior comparative effectiveness over best supportive care was reasonable.
- 6.33 The PBAC considered that olaparib demonstrated inferior comparative safety compared to sequential NHA use or BSC.

Economic analysis

- 6.34 The submission presented a stepped economic evaluation based on the PROfound trial, comparing olaparib to NHA. A cost-utility analysis using a partitioned survival model with three health states was provided. The table below provides a summary of model components.

Table 11: Summary of model structure and rationale

Component	Summary
Time horizon	Lifetime (10 years)
Outcomes	Progression-free years gained, life-years gained, quality-adjusted life-years gained, AEs
Methods used to generate results	Partitioned survival model
Health states	Progression free (PF); progressed disease (PD); death
Utilities	Based on EQ-5D-5L values from PROfound; disutility for AEs and SREs from PROfound
Cycle length	Monthly
Transition probabilities	No specific transition probabilities were modelled; health state allocation was determined by rPFS and OS curves, which were based on PROfound data with extrapolation
PROfound population – data sources	rPFS: <i>BRCA1/2</i> subgroup of PROfound OS: <i>BRCA1/2</i> subgroup of PROfound, adjusted for treatment switching AEs: Cohort A + B of PROfound Utilities: Cohort A (ITT population)
Test parameters	A test + drug model was not provided
False positives/negatives	Not included

Source: Table 3.1, p154 of the submission.

AE= adverse events OS = overall survival; rPFS = radiological progression-free survival; SRE = skeletal-related events.

6.35 A summary of the key drivers of the model is provided in the table below.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Model comparator	The nominated comparator of subsequent NHA was not appropriate and does not reflect the Australian setting. Subsequent NHA is likely to have minimal activity due to cross resistance.	Likely high (however effect not able to be fully tested).
OS evidence used in the model	The applied adjusted HR of [REDACTED] ² was significantly lower than unadjusted results for the same subgroup (0.63) and the ITT (0.69).	High, favours olaparib. Using the unadjusted HR, increased the ICER to \$[REDACTED] ¹ /QALY.
Adjustment for treatment switching	The use of the RPSFTM to adjust for treatment switching may not have been the most appropriate method to use as PROfound is unlikely to meet the common treatment effect assumption that underlies RPSFTM analyses. In addition, the ESCs advised that recensoring should not be used. Without recensoring the OS HR for the <i>BRCA1/2</i> subgroup, using the RPSFTM method (Cox proportional hazards model), increased to [REDACTED] ² .	High, favours olaparib (as above)
Utilities	While the utility values were trial-based, the ESCs considered that they were high compared to other estimates in the literature (0.7532 for progression-free survival and 0.7034 for progressed disease). The submission also applied the same values to olaparib and NHA-treated patients, which may not be reasonable given more AEs are expected with olaparib treatment. The PSCR stated that decrements in utility due to AEs were captured via an AE-related disutility applied in the model (-0.0393 for olaparib and 0.0218 for NHAs).	Moderate, favours olaparib

Source: Compiled during the evaluation.

AE = adverse event; *BRCA* = breast cancer gene; CI = confidence interval; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; NHA = novel hormonal agent; OS = overall survival; PSCR = pre-Sub-Committee Response; QALY = quality adjusted life year; RPSFTM = rank preserving structural failure time model.

The redacted values correspond to the following ranges:

¹\$135,000 to < \$155,000

²Adjusted OS hazard ratio: manuscript submitted to *European Urology* for publication.

6.36 The results of the stepped economic evaluation are provided in the following table.

Table 13: Results of the stepped economic evaluation

Step and component	Olaparib	NHA	Increment
Step 1: trial-based - 36 month time horizon			
Costs	\$ [redacted]	\$21,714	\$ [redacted]
PFLY	0.841	0.280	0.561
LY	1.708	0.742	0.966
Incremental cost/extra PFLY gained			\$ [redacted] ¹
Incremental cost/extra LY gained			\$ [redacted] ²
Step 2: trial-based - 36 month time horizon with AE and SRE cost			
Costs	\$ [redacted]	\$24,685	\$ [redacted]
PFLY	0.841	0.280	0.561
LY	1.708	0.742	0.966
Incremental cost/extra PFLY gained			\$ [redacted] ¹
Incremental cost/extra LY gained			\$ [redacted] ²
Step 3: trial-based - 36 month time horizon with utilities (first-line treatment) and AE and SRE cost			
Costs	\$ [redacted]	\$24,685	\$ [redacted]
QALY	1.186	0.510	0.676
Incremental cost/extra QALY gained			\$ [redacted] ³
Step 4: 10-year time horizon with utilities and discounted costs			
Costs	\$ [redacted]	\$52,882	\$ [redacted]
LY	1.821	0.790	1.03
Incremental discounted cost/extra LY gained (base case)			\$ [redacted] ³
QALY	1.223	0.471	0.751
Incremental discounted cost/extra QALY gained			\$ [redacted] ¹

Source: Table 3.29 of the submission.

AE = adverse event; LY = life year; NHA = novel hormonal agent; PFLY = progression-free life year; QALY = quality adjusted life year; SRE = skeletal-related event.

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$25,000 to < \$35,000

³ \$35,000 to < \$45,000

6.37 The modelled economic evaluation over a period of 10 years estimated an incremental cost/QALY of \$45,000 to < \$55,000. Although the PROfound trial demonstrated that olaparib treatment results in an overall survival advantage, the ESCs considered that the ICER did not accurately represent the cost-effectiveness of olaparib in mCRPC patients with *BRCA1/2* pathogenic variants, as:

- The comparator (NHAs) in the model was inconsistent with their PBS restrictions. Sensitivity analyses in which the costs associated with NHA treatment in the comparator arm were removed are presented below.
- For OS, the model was based on the *BRCA1/2* subgroup of PROfound, adjusted for treatment switching. The use of RPSFTM and application of recensoring to adjust for treatment switching may not have been appropriate. The change in point

estimate with adjustment for switching (HR changed from 0.63 to ■■■⁹) was considerable. Sensitivity analysis showed the model was sensitive to use of adjustment for treatment switching, with the ICER increasing from \$45,000 to < \$55,000/QALY to \$135,000 to < \$155,000/QALY when unadjusted OS data was used. The ESCs advised that the use of RPSFTM without recensoring may be preferable.

- Costs applied in the model were not likely to be accurate. Testing costs were inappropriately applied to 67% of patients in the NHA arm to account for patients who switched to olaparib treatment in the PROfound trial. In addition, the submission did not consider germline testing in patients with a positive *BRCA1/2* somatic test, or cascade testing of family members.
- While the utility values were trial-based, they appeared high for mCRPC patients (0.7532 for progression-free survival and 0.7034 for progressed disease). A 'time to death' disutility was applied (for death within 1 year, value depended on proximity to death) although the ICER was not sensitive to this variable, its use was not explained or justified by the submission.
- The model applied an exponential distribution to time on treatment from PROfound. The time on treatment extrapolations were based on the combined Cohort A and Cohort B populations, which were not representative of the model population (patients with *BRCA1/2* pathogenic gene variants). Further, the submission's extrapolation of time on treatment, which used an exponential distribution, resulted in patients being available for treatment for longer than they were predicted to be alive by the model (2.7 years longer for olaparib-treated patients and 2.6 years longer for NHA-treated patients). While treatment costs were not applied once patients were no longer alive, the extrapolation used did not seem to accurately estimate treatment duration. Further, the time on treatment extrapolations were based on the June 2019 data cut of PROfound; whereas, the OS extrapolations were based on the March 2020 data cut. The pre-PBAC response noted that the sensitivity analysis in which patients were assumed to be treated until disease progression in both arms, which would overestimate the duration of treatment as many patients cease treatment prior to progression or experience dose interruptions, increased the ICER to \$55,000 to < \$75,000/QALY.

- 6.38 Consideration of various *BRCA1/2* and olaparib funding scenarios (test funded by MBS and treatment funded by PBS, respectively) was not possible given the submission did not provide a test and treatment model, and as the model assumed all patients had a *BRCA1/2* pathogenic gene variant.

⁹ Adjusted OS hazard ratio: manuscript submitted to *European Urology* for publication.

Table 14: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change ICER
Base case	\$ [REDACTED]	0.751	\$ [REDACTED] ¹	-
OS data (base case: <i>BRCA1/2</i> HR = [REDACTED] ^a adjusted for treatment switching)				
Not adjusted for treatment switching (HR = 0.63)	\$ [REDACTED]	0.275	\$ [REDACTED] ²	+166.3%
Comparator arm (NHA) treatment costs (base case: \$ [REDACTED])				
Removal of comparator arm (NHA) costs	\$ [REDACTED]	0.751	\$ [REDACTED] ³	+54.7%
Utility values (base case: PROfound; 0.7532 for PF, 0.7034 for post-progression based on time to death)				
Literature (0.7150 PF; 0.5380 post-progression)	\$ [REDACTED]	0.654	\$ [REDACTED] ⁴	+15.0%
Based on progression status (0.7261, 0.6642)	\$ [REDACTED]	0.719	\$ [REDACTED] ¹	+4.5%
Treatment discontinuation (base case: median treatment duration)				
Treated until progression	\$ [REDACTED]	0.751	\$ [REDACTED] ⁴	+17.6%
Time horizon (base case: 10 years)				
5 years	\$ [REDACTED]	0.751	\$ [REDACTED] ¹	-0.3%
Multivariate analyses				
Treated until progression and utility values based on progression status	\$ [REDACTED]	0.719	\$ [REDACTED] ⁴	+23.0%
Treated until progression and literature-based utility values	\$ [REDACTED]	0.654	\$ [REDACTED] ⁴	+35.3%
OS HR not adjusted for treatment switching and removal of comparator arm (NHA) costs	\$ [REDACTED]	0.275	\$ [REDACTED] ⁵	+319.8%
OS HR not adjusted for treatment switching, removal of comparator arm (NHA) costs and utility values based on progression status	\$ [REDACTED]	0.270	\$ [REDACTED] ⁵	+327.4%

Source: Table 3.34 of the submission.

BRCA1/2 = breast cancer genes 1 and 2; HR = hazard ratio; ICER = incremental cost effectiveness ratio; NHA = novel hormonal agents; OS = overall survival; PF = progression free; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000 /QALY

² \$135,000 to < \$155,000 /QALY

³ \$75,000 to < \$95,000 /QALY

⁴ \$55,000 to < \$75,000 /QALY

⁵ \$155,000 to < \$255,000 /QALY

^a Adjusted OS hazard ratio: manuscript submitted to *European Urology* for publication.

6.39 The ESCs considered that the revisions required to the economic evaluation, which included concerns regarding the comparator, the use of adjusted OS inputs, inconsistencies with the time to treatment extrapolations, the utility values applied and the lack of a test and treatment model structure were complex and would require re-evaluation.

Drug cost/patient/course: \$ [REDACTED]

6.40 The following table outlines the drug cost per patient for both olaparib and NHA across the model and the financial estimates.

Table 15: Drug and test cost per patient

	Olaparib			NHA ^a		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean dose	600 mg/day	600 mg/day	600 mg/day	Abi: 160 mg/day Enz: 1,000 mg/day	Abi: 160 mg/day Enz: 1,000 mg/day	Not included
Mean duration	242.8 days ^b	243 days (median)	227 days ^c (median)	146.3 days ^b	136 days (median)	
Total mg administered	133,312 mg	NC	NC	Abi: 23,015 mg Enz: 139,570 mg	NC	
Cost/patient/month	-	\$ [REDACTED] ^d	\$ [REDACTED] ^e	-	\$ [REDACTED] ^f	
Cost/patient/course	-	\$ [REDACTED] ^g	\$ [REDACTED] ^h	-	\$ [REDACTED] ^g	

Source: Table 3-15 of the submission; worksheet 'Event Mgmt Cost' in the Excel workbook Olaparib mCRPC CEM.

Abi = abiraterone; DPMQ = dispensed price for maximum quantity; Enz = enzalutamide; NC = not calculable; NHA = novel hormonal agent.

^a The submission assumed that 55% of patients would take abiraterone, and 45% would take enzalutamide.

^b Duration of treatment was only available for Cohort A and Cohort B combined of PROfound. When dose interruptions were included in the calculation of treatment duration, the mean duration of treatment became 229.6 days for olaparib and 143.7 days for NHA.

^c The submission assumed that 5% of patients would have a dose reduction and use the 100 mg dose of olaparib. While the submission identified that the first dose reduction is to 500 mg/day and the second is to 400 mg/day, there was no information provided on how many patients would use 500 mg or 400 mg, or how long each would be used. Thus, the total mg used over 227 days cannot be determined.

^d A dose intensity of 91.51% was assumed by the submission, based on PROfound data. The cost per month in the model was adjusted for cost over a treatment cycle (4 weeks) to a one month period.

^e The same DPMQ was applied to the 150 mg and 100 mg doses of olaparib, and the submission assumed that usage of the 100 mg dose would be 5%, to account for dose reductions.

^f A dose intensity 98.32% was applied to abiraterone, and a dose intensity of 95.40% was applied to enzalutamide. The abiraterone cost also included the cost of concomitant prednisolone.

^g The submission included test cost as part of drug cost, however test cost has been removed from drug cost for the values reported here.

^h This was calculated based on the cost of patients treated in Year 1, divided by the number receiving initial treatment and the number receiving continuing treatment. Copayment cost has been subtracted.

6.41 The cost of olaparib treatment based on the economic model (\$ [REDACTED]) could not be associated with a treatment duration as the economic model predicted treatment duration of 2.7 years longer than a patient was alive in the model. The cost for olaparib based on the financial estimates applied 5% usage of the 100 mg dose to account for dose reductions, but no information was provided on what dose reduction was used (to 400 mg/day or 500 mg/day) or for how long the dose reduction lasted. The submission provided no discussion as to why dose intensity was applied in the economic model but a dose reduction was applied in the financial estimates.

Estimated PBS & financial implications

6.42 This submission was not considered by DUSC. While the submission stated that patient population estimates in the ratified PICO for Application 1618 were based on an incident prostate cancer population, the submission based its estimates of use on a prevalent population. The submission stated that the literature supports the assertion that the prevalent population is the main source of patients for the requested listing because patients with prostate cancer typically progress to mCRPC over a number of years. The key inputs and literature sources used in the financial estimates are summarised in the table below.

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Table 16: Data sources and parameters used to calculate the financial impact of the requested listing of olaparib for mCRPC

Data	Value and source	Comment																		
Prevalent population																				
HSPC patients	<table><tr><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Year 6</th></tr><tr><td>1</td><td>1</td><td>1</td><td>2</td><td>2</td><td>2</td></tr></table> Assumed to increase 5% per year, based on a HSPC population and its increase in size in 2020 from 2019.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	1	1	1	2	2	2	The submission did not consider that the HSPC population had varied considerably in growth over the past 10 years, with growth rates ranging from 0% to 6.3%. As such, the PBAC considered that the assumed 5% yearly increase in the prevalent population may not be accurate and was likely overestimated.						
Year 1	Year 2	Year 3	Year 4	Year 5	Year 6															
1	1	1	2	2	2															
Progression to CRPC	<table><tr><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Year 6</th></tr><tr><td>17.8%</td><td>17.8%</td><td>17.8%</td><td>17.8%</td><td>17.8%</td><td>17.8%</td></tr><tr><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td></tr></table> Alemayehu 2010.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	17.8%	17.8%	17.8%	17.8%	17.8%	17.8%	3	3	3	3	3	3	The assumption that 17.8% of HSPC patients will progress to CRPC, based on data from Alemayehu (2010), was not likely to represent the development of CRPC in clinical practice. The 17.8% value calculated by the submission was based on 4 patients with likely (N=4) or known (N=5) CRPC divided by 6 possible CRPC patients. The submission did not indicate why patients with 'likely' CRPC were included in the calculation. The PBAC noted that if the proportion was based on patients with actual CRPC, it would be 2.3%, thereby decreasing patient numbers.
Year 1	Year 2	Year 3	Year 4	Year 5	Year 6															
17.8%	17.8%	17.8%	17.8%	17.8%	17.8%															
3	3	3	3	3	3															
mCRPC	<table><tr><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Year 6</th></tr><tr><td>92%</td><td>92%</td><td>92%</td><td>92%</td><td>92%</td><td>92%</td></tr><tr><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td></tr></table> Based on Kwan 2019.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	92%	92%	92%	92%	92%	92%	3	3	3	3	3	3	Kwan (2019) was a retrospective review of treatment of 137 Australian CRPC patients. The publication noted that 8% of patients had non-metastatic disease. The submission then assumed that the remaining 92% of patients had mCRPC, which may not be accurate. The submission considered alternate rates of 84% and 95% (used in the PICO) in sensitivity analyses. The PBAC considered that this value was likely overestimated.
Year 1	Year 2	Year 3	Year 4	Year 5	Year 6															
92%	92%	92%	92%	92%	92%															
3	3	3	3	3	3															
Uptake BRCA1/2 test	<table><tr><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Year 6</th></tr><tr><td>80%</td><td>82.5%</td><td>85%</td><td>87%</td><td>88.5%</td><td>90%</td></tr><tr><td>4</td><td>4</td><td>3</td><td>3</td><td>3</td><td>3</td></tr></table> Based on uptake from current indications.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	80%	82.5%	85%	87%	88.5%	90%	4	4	3	3	3	3	The use of genetic testing was based on the sponsor's experience. No information was provided as to the specific source of the initial proportion (80%), but it corresponded to the proportion cited in the PICO. The submission stated testing would increase with clinical experience.
Year 1	Year 2	Year 3	Year 4	Year 5	Year 6															
80%	82.5%	85%	87%	88.5%	90%															
4	4	3	3	3	3															
BRCA1/2 variant detected	<table><tr><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Year 6</th></tr><tr><td>9.7%</td><td>9.7%</td><td>9.7%</td><td>9.7%</td><td>9.7%</td><td>9.7%</td></tr><tr><td>5</td><td>5</td><td>4</td><td>4</td><td>4</td><td>4</td></tr></table> Based on PROfound data.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	5	5	4	4	4	4	Detection of BRCA1/2 pathogenic gene variants was sourced from the PROfound trial. The PBAC noted that the calculation to determine the value of 9.7% could not be verified, and was likely overestimated when compared to incidence rates of 5.7% when the sequenced population of PROfound was used and 3.6% when the whole screened population of PROfound was used.
Year 1	Year 2	Year 3	Year 4	Year 5	Year 6															
9.7%	9.7%	9.7%	9.7%	9.7%	9.7%															
5	5	4	4	4	4															
NHA treatment – eligible patients	<table><tr><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Year 6</th></tr><tr><td>79%</td><td>81%</td><td>83%</td><td>85%</td><td>86.25%</td><td>87.25%</td></tr><tr><td>5</td><td>5</td><td>5</td><td>5</td><td>4</td><td>4</td></tr></table> Given the numbers with a BRCA1/2 pathogenic gene variant identified, the submission assumed those who had received NHA treatment would be eligible for olaparib.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	79%	81%	83%	85%	86.25%	87.25%	5	5	5	5	4	4	The submission stated that the proportion of patients receiving NHA treatment was based on 2019 PBS data. The PBAC noted that the cited proportions may not accurately reflect eligible patients, as the requested restriction specifies that patients must have progressed on or failed NHA treatment, while the cited proportions appear to represent all treated patients. The submission gave no indication of the
Year 1	Year 2	Year 3	Year 4	Year 5	Year 6															
79%	81%	83%	85%	86.25%	87.25%															
5	5	5	5	4	4															

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Data	Value and source	Comment
		proportion who would fail treatment, and thus be eligible for olaparib. The PBAC also noted that the estimates should reflect the number of patients expected to have an ECOG performance status 0-2.
Treated patients		
Uptake and continuation	Uptake of 95% across Years 1 to 6 was a submission assumption; continuation of 86% was sourced from PROfound. Treatment duration was 227 days, sourced from PROfound, with a 95% compliance applied.	The submission considered an alternate uptake rate of 80% in a sensitivity analysis. The claimed source of continuation (86%; <i>BRCA1/2</i> PFS at 3 months) could not be verified. Values of 81% and 91% were considered by the submission in sensitivity analyses. Treatment duration was sourced from Cohort A+B of PROfound, which was not representative of the proposed PBS population. The PBAC considered that treatment duration should be based on that of the <i>BRCA1/2</i> subgroup of Cohort A (i.e. 290.2 days) and the same compliance as applied in the economic model (i.e. 91.51%) should be used.
Costs		
<i>BRCA1/2</i> test	Tumour test: \$960 (80% rebate) Sample retrieval: \$68 (80% rebate) Germline test: \$960 (80% rebate)	As per existing <i>BRCA1/2</i> MBS items (73301; 73295) and existing sample retrieval item (72860).
Olaparib	\$ - requested price	-
Patient copayment	PBS: \$11.79; RPBS: \$5.27 PBS statistics for abiraterone and enzalutamide (Jan 2019 to Dec 2019).	

Source: Table 4.2.2, Table 4.2.5, Section 4.2.1.2 to Section 4.2.1.5 of the submission.

BRCA1/2 = breast cancer genes 1 and 2; CRPC = castration resistant prostate cancer; HSPC = hormone sensitive prostate cancer; MBS = Medicare Benefits Schedule; mCRPC = metastatic castration resistant prostate cancer; NHA= novel hormonal agent; PBS = Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

¹ 30,000 to < 40,000

² 40,000 to < 50,000

³ 5,000 to < 10,000

⁴ 500 to < 5,000

⁵ < 500

⁶ \$15,000 to < \$25,000

6.43 The estimated test and patient numbers, script numbers and costs for the PBS listing of olaparib and MBS listing of the *BRCA1/2* pathogenic gene variant test are provided below.

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Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of BRCA1/2 pathogenic gene variant test						
Number of patients tested	1	1	2	2	2	2
Number likely to receive a positive test result	3	3	1	1	1	1
Estimated extent of use of olaparib						
Patients initiated	3	3	3	3	3	1
Grandfathered	3					
Patients continuing	3	3	3	3	3	3
Number of scripts ^a	1	1	1	1	1	1
Estimated financial implications of the BRCA1/2 pathogenic gene variant test to the MBS						
Net cost to MBS	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Estimated financial implications of olaparib to the PBS/RPBS						
Cost to PBS/RPBS	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Patient copayment	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4
Net cost to PBS/RPBS	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Net financial implications						
Net cost to PBS/RPBS/MBS	\$ 5	\$ 5	\$ 5	\$ 5	\$ 5	\$ 5

Source: Table 4.2.5, Table 4.2.6, Table 4.2.7, Table 4.2.9, Table 4.5.4 and Table 4.5.5 of the submission; worksheet '7. Net changes – MBS'; worksheet '2b. Patients – prevalent' of the Excel workbook 'Olaparib in mCRPC_Section_4_Workbook_Final'.

BRCA1/2 = breast cancer genes 1 and 2; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Assuming a treatment duration of 227 days, with 2.85 scripts for initial treatment and 4.85 scripts for continuing treatment as estimated by the submission.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ < 500

⁴ \$0 to < \$10 million

⁵ \$10 million to < \$20 million

6.44 The estimated net cost to Government was \$90 million to < \$100 million over the first 6 years of listing. This was evenly split between PBS/RPBS costs (\$40 million to < \$50 million) and MBS costs (\$40 million to < \$50 million). The ESCs considered that the submission's estimates were uncertain, for the following reasons:

- Patient numbers were not likely to be accurate, given use of a prevalent population that has not been accurately defined. This would likely overestimate the CRPC population and the proportion of patients who have progressed or failed on NHA treatment.
- Given the above, script numbers were not likely to be accurate. The accuracy of the script numbers was further impacted by the assumption that treatment will last for 227 days, which was sourced from the Cohort A + B population and therefore, potentially not representative of treatment duration in BRCA1/2 patients. The submission also assumed 95% compliance with treatment. Further, the submission provided no explanation as to why a strategy of dose reduction was used (5% of patients had a dose reduction for the entire treatment period), when the economic

model applied a dose intensity of 91.51%. The pre-PBAC response provided revised financial impact estimates which applied a mean total treatment duration of olaparib of 290.2 days, sourced from the *BRCA1/2* population, and a compliance rate of 91.51%. The change to the net cost to the PBS/RPBS was minimal.

- Estimated costs for testing were based on patient numbers, which, as noted above, were not likely to be accurate. Further, the submission appeared to not include the test cost for the 9% of patients who do not have a tissue sample available. This would underestimate the cost.
- 6.45 It could not be determined if the net financial implications were over or underestimated. Although there were indications patient numbers were overestimated, there were also indications that test numbers may be underestimated, and script numbers could not be accurately determined.
- 6.46 The use of a combined incident/prevalent approach to determine patient numbers may have provided more accurate estimates. It would have been reasonable for the submission to use the following steps:
- Project an annual number of incident patients over each year of the forward estimates.
 - Assume a prevalent pool of untreated patients with mCRPC who would initiate treatment in the first year of listing for olaparib.
 - Estimate continuing patients for each yearly initiating cohort, including the prevalent pool in the Year 1 initiating cohort, over the forward estimates.
- 6.47 The PSCR stated that the use of a prevalent population was considered appropriate as prostate cancer is a long term condition and patients progress to mCRPC over a variable number of years, and therefore, the use of the incident population is not relevant. Acknowledging the difficulty in estimating the annual incidence of patients whose prostate cancer progresses to the stage at which olaparib would be considered, the PBAC considered that a combined incident/prevalent approach would provide additional confidence in the financial estimates.

Quality use of medicines

- 6.48 The submission stated that *BRCA* testing to inform treatment decisions with olaparib in patients with mCRPC may potentially result in a delay in patients obtaining their test result, possibly due to sample retrieval or the need for rebiopsy. The submission indicated that the sponsor has undertaken to work to facilitate the development of educational and information resources that allow for the identification of *BRCA1/2* pathogenic gene variants in a timely fashion. These included healthcare professional and patient information on *BRCA1/2* testing and clinician training.

Financial management – risk sharing arrangements

- 6.49 The submission stated that the sponsor would be willing to discuss an appropriate risk share arrangement (RSA) upon receiving a positive recommendation from the PBAC. The submission provided no further information on the content of the possible RSA.

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

7 PBAC outcome

- 7.1 The PBAC did not recommend olaparib for the treatment of metastatic castration resistant prostate cancer (mCRPC) in patients with pathogenic or likely pathogenic *BRCA1/2* gene variants. The PBAC considered that although olaparib demonstrated clinical benefit in patients with *BRCA1/2* gene variants, the nominated comparator did not reflect current Australian clinical practice which meant that the economic evaluation was highly uncertain.
- 7.2 The PBAC welcomed the input from the two organisations via the Consumer Comments facility which noted that the use of olaparib may improve patients' quality of life.
- 7.3 The PBAC noted the proposed clinical algorithm placed olaparib as later line therapy for mCRPC with *BRCA1/2* pathogenic variants following the use of a novel hormonal agent (NHA). The PBAC considered that the appropriate clinical place for olaparib was as 3L treatment following failure on docetaxel and failure on an NHA.
- 7.4 The PBAC noted that the submission nominated physician's choice of NHA (i.e. abiraterone or enzalutamide) as the primary comparator. The PBAC recalled that it had previously recommended that the sequential use of NHAs was not appropriate due to cross-resistance and noted that the current PBS listing criteria for the NHAs explicitly prevents the sequential use of NHAs. The PBAC considered that cabazitaxel, which is currently PBS listed for use following docetaxel, and best supportive care (BSC) would be the appropriate comparators. In addition, the PBAC considered that docetaxel would also be an appropriate comparator where patients had not previously received docetaxel.
- 7.5 The PBAC noted that the submission was based on one open-label, randomised controlled trial, the PROfound trial, which compared olaparib to either abiraterone or enzalutamide in patients with mCRPC who had progressed on a previous NHA. The PBAC noted that the majority of the key efficacy outcomes were based on the results of the subgroup of Cohort A of the PROfound trial which included patients with *BRCA1/2* pathogenic gene variants. Safety outcomes were based on the combined results of Cohorts A and B (Cohort B included patients with pathogenic variants in 12 other genes).

- 7.6 The PBAC noted that for the primary outcome of radiological progression free survival (rPFS) in Cohort A patients, olaparib demonstrated a statistically significant advantage compared to NHA therapy (HR = 0.34; 95% CI: 0.25, 0.47). For the subgroup of patients in Cohort A with *BRCA1/2* gene variants, the advantage was numerically greater (HR = 0.22; 95% CI: 0.15, 0.32). The HR for PFS for the *ATM* positive subgroup was 1.04 (95% CI: 0.61, 1.87), with a test for interaction across the subgroups yielding a p-value of <0.0001. The PBAC considered this was a reasonable basis on which to accept the *BRCA1/2* subgroup results over the ITT results from Cohort A of PROfound.
- 7.7 The PBAC noted that in terms of overall survival, olaparib patients in Cohort A demonstrated a 4.4 month median incremental gain over NHA patients (HR = 0.69; 95% CI: 0.50, 0.97). For patients in the *BRCA1/2* subgroup of Cohort A, the median incremental gain was 5.7 months (HR = 0.63; 95% CI: 0.42, 0.95).
- 7.8 The PBAC noted that 67.5% of patients in the NHA arm of Cohort A received subsequent treatment with olaparib. The PBAC noted that the submission adjusted for this treatment switching using the RPSFTM with recensoring which resulted a hazard ratio of [REDACTED]¹⁰ for patients with the *BRCA1/2* gene variant. Using the RPSFTM without recensoring resulted in a hazard ratio of [REDACTED]¹⁰. Given the two statistical approaches used to adjust for switching (RPSFT models with and without recensoring) produced materially different HRs, there was material uncertainty about the treatment effect for OS used in the economic model.
- 7.9 Considering that the majority of patients in Cohort A of the PROfound trial had progressed following an NHA, and given the lack of evidence supporting the efficacy of sequential NHA use, the PBAC considered that the comparator in the PROfound trial, i.e. an NHA, was a reasonable proxy for BSC. Therefore, the PBAC concluded that olaparib was superior compared to best supportive care (BSC) in terms of efficacy. The PBAC considered that the incremental benefit of olaparib versus cabazitaxel was unknown.
- 7.10 In terms of safety, the PBAC noted that olaparib was associated with significantly greater proportions of patients experiencing any adverse event (AE), AEs ≥ Grade 3, serious AEs, AEs leading to discontinuation, AEs leading to dose reduction and AEs leading to dose interruption compared to sequential NHA use. The PBAC considered that olaparib was inferior in terms of safety compared to BSC.
- 7.11 The PBAC noted that the submission presented a cost utility analysis comparing olaparib with an NHA, based on the *BRCA1/2* subgroup of Cohort A of the PROfound trial. The PBAC considered that the resultant incremental cost effectiveness ratio

¹⁰ Adjusted OS hazard ratio: manuscript submitted to European Urology for publication.

(ICER) of \$45,000 to < \$55,000 per QALY was difficult to assess and highly uncertain due to a number of issues, including:

- the model did not reflect the codependent nature of the submission by providing a test and drug model to assess the consequences of less than perfect test performance (the PBAC noted that incorporation of the costs and subsequent health outcomes of further germline testing in patients with a positive *BRCA1/2* somatic test result, or of cascade testing of family members were matters for MSAC);
- the inappropriate application of NHA use as the comparator. The PBAC considered that the comparators should be cabazitaxel or BSC. The PBAC noted that if NHA use was considered to be a proxy for BSC, the costs associated with NHA use should be removed;
- the application of a 10-year time horizon. The PBAC considered that a 5-year time horizon would more appropriately represent later-line mCRPC treatment;
- that testing costs were inappropriately applied to the 67% of patients in the NHA arm who switched to olaparib treatment in the PROfound trial. The PBAC noted that these costs were appropriately removed in the pre-PBAC response;
- that the model applied the overall survival hazard ratio adjusted for treatment switching and with recensoring ($HR = \text{[REDACTED]}$)¹¹ without sufficient justification of the method selected. The PBAC noted that the change in the point estimate was considerable when compared to the unadjusted value ($HR = 0.63$) and the adjusted value from the RPSFT model without recensoring ([REDACTED])¹¹; the model was highly sensitive to this adjustment;
- that time on treatment extrapolations were based on the combined Cohort A and Cohort B populations, which were not representative of the model population and which resulted in patients being available for treatment for longer than they were predicted to be alive; and
- the utility values, although trial based, were high compared to other estimates in the literature.

7.12 The PBAC noted that calculation of the prevalence of *BRCA1/2* as reported in the submission (9.7% = 1% *BRCA1* and 8.7% *BRCA2*) based on the PROfound trial could not be verified from the trial data. The submission stated that this value was a weighted average of tumour testing and germline results, however the number of patients identified with *BRCA1* and/or *BRCA2* pathogenic variants and the denominator for

¹¹ Adjusted OS hazard ratio: manuscript submitted to *European Urology* for publication.

determining the prevalence (and their source) were unclear. The PBAC also noted that estimates of prevalence from the literature varied and that it was possible for a patient to have both a *BRCA1* pathogenic variant and a *BRCA2* pathogenic variant. The PBAC requested that MSAC advise on the likely prevalence in the Australian population with metastatic castration resistant prostate cancer of having a *BRCA1* pathogenic variant and/or a *BRCA2* pathogenic variant.

- 7.13 In addition to uncertainty regarding the prevalence of *BRCA1/2*, the PBAC considered that the estimated utilisation and financial impact of listing olaparib was likely overestimated and uncertain due to the reasons outlined in Table 16.
- 7.14 The PBAC considered that a resubmission for olaparib should address the issue with the comparator; respecify the economic model further as outlined in paragraphs 6.39 and 7.11 and then present an ICER of less than \$55,000 to < \$75,000 per QALY; and present revised estimates of utilisation and financial implications which incorporate the advice as outlined in Table 16. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

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.