7.04 OLAPARIB,  
Tablet 100 mg,   
Tablet 150 mg,  
Lynparza ®,  
AstraZeneca Pty Ltd.

1. Purpose of submission
   1. The Standard Re-entry resubmission requested an 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).
   2. Listing was requested on the basis of a cost-minimisation approach versus talazoparib plus enzalutamide, on the assumption that talazoparib plus enzalutamide would proceed to PBS listing for the same indication. Alternatively, the listing was also requested on the basis of a cost-effectiveness analysis versus NHA monotherapy.

**Table 1: Key components of the clinical issue addressed by the resubmission**

|  |  |
| --- | --- |
| **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 (OLA) 300 mg (2×150 mg) twice daily (total dose 600 mg/day) in combination with abiraterone (ABI) once daily plus corticosteroid (two formulations: abiraterone 1g/day + prednisone/prednisolone 10 mg/day and abiraterone 500mg/day + methylprednisolone 8mg/day) |
| Comparator | Main (primary) comparator: Talazoparib (TAL) 0.5 mg once daily a in combination with enzalutamide (ENZ) 160 mg once daily  Secondary comparator: NHA monotherapy (either abiraterone or enzalutamide) |
| Outcomes | OS, PFS, PROs, safety, AEs |
| Clinical claim | The combination of olaparib plus abiraterone demonstrates non-inferior efficacy and superior safety when compared to talazoparib plus enzalutamide in NHA-naïve mCRPC patients with a confirmed *BRCA*1 or *BRCA*2 pathogenic variant. The PSCR revised the claim of superior safety, stating that a claim of non-inferior safety may be more appropriate.  The combination of olaparib plus abiraterone demonstrates superior efficacy and inferior safety when compared to ABI plus placebo in NHA-naïve mCRPC patients with a confirmed *BRCA*1 or *BRCA*2 pathogenic variant. |

Blue shading represents information previously considered by the PBAC.

Source: Table 1-3, p36 of the resubmission.

ABI=abiraterone; AE=adverse events; *BRCA*=breast cancer gene; ENZ=enzalutamide; mCRPC=metastatic castration- prostate cancer; NHA=novel hormonal agent; OLA=olaparib; OS=overall survival; PFS=progression-free survival; PRO=patient reported outcomes; TAL=talazoparib, PSCR = Pre-Sub-Committee Response

a TAL dose reduction may be required to manage adverse events; TAL 0.1 mg, 0.25 mg and 0.35 mg capsules allow for dose reductions.

1. Background

***Registration status***

* 1. Olaparib in combination with abiraterone and prednisone/prednisolone was TGA registered in October 2023 for treatment of adult patients who have metastatic castration-resistant prostate cancer with a deleterious or suspected deleterious *BRCA* mutation (germline or somatic).

***Previous PBAC consideration***

* 1. At the November 2023 PBAC Meeting, the PBAC did not recommend olaparib, for use in combination with abiraterone, for the treatment of mCRPC patients with *BRCA1/2* pathogenic variants who have not received prior treatment with a NHA.
  2. The PBAC subsequently considered talazoparib in combination with enzalutamide for the same indication, at the March 2024 and July 2024 PBAC Meetings. The PBAC recommended the PBS listing for talazoparib plus enzalutamide at the July 2024 PBAC Meeting.
  3. This resubmission, for olaparib plus abiraterone, was written in anticipation that the PBAC would recommend talazoparib plus enzalutamide for the treatment of mCRPC patients with *BRCA1/2* pathogenic variants who have not received prior treatment with a NHA. Talazoparib plus enzalutamide was nominated as a near-market comparator in the November 2023 PBAC submission for olaparib plus abiraterone, given both regimens consist of a poly ADP-ribose polymerase inhibitor (PARPi) and a NHA. Hence, the main change in this re-submission was the nomination of talazoparib plus enzalutamide as the main comparator (rather than monotherapy with a NHA) and the presentation of a cost-minimisation analysis (rather than a cost-utility analysis). However, the resubmission also aimed to address the key matters of concern raised by the PBAC at the November 2023 PBAC Meeting, given monotherapy with a NHA remained a relevant comparator until talazoparib plus enzalutamide becomes available to patients. Table 2 presents a summary of key matters of concern raised by the PBAC at the November 2023 PBAC Meeting and how the matters were addressed in the resubmission.

**Table 2: Summary of key matters of concern**

| **Component** | **Matter of concern** | **How the resubmission addresses it** |
| --- | --- | --- |
| Clinical evidence | The clinical evidence presented in the submission, which was based on a small *post hoc* subgroup, was uncertain (paragraph 7.1, olaparib PSD, November 2023). | Partially addressed.  The resubmission included additional evidence from a supportive trial BRCAAWAY. The BRCAAWAY trial, however, was also based on small numbers (n=40 in the relevant treatment arms) and prognostic factors were not well balanced across treatment arms at baseline. |
| Clinical place | The clinical place of olaparib plus abiraterone was uncertain, noting that olaparib was available as monotherapy in the mCRPC setting following treatment with an 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 (paragraph 7.1, olaparib PSD, November 2023). | Partially addressed.  The resubmission stated that as the BRCAAWAY trial permitted cross over, which provided direct evidence comparing combination therapy to sequential treatment with NHA and olaparib monotherapy and showed substantial improvements in outcomes. The proportion of patients who crossed over from abiraterone to olaparib was only 42% (8/19 patients). Hence, this trial was not sufficiently powered to compare combination to sequential treatment. |
| Economic evaluation | The PBAC considered that ICER was highly uncertain and likely underestimated (paragraph 7.1, olaparib PSD, November 2023). | Partially addressed.  The resubmission, similar to the pre-PBAC response, reduced the time horizon, adopted more conservative extrapolation functions, and lowered the proposed price for olaparib. Additionally, the resubmission updated the utility for the progressive disease health state. As a result, the new ICER was 2.5% higher than the estimate proposed in the November 2023 submission. |
| Financial impact | The PBAC considered that the financial impact estimates were overestimated (paragraph 7.1, olaparib PSD, November 2023). | Partially addressed.  The resubmission updated its assumptions regarding the number of incident NHA-naïve patients in first line mCRPC, now assuming they progress exclusively from m0HSPC. Additionally, it revised the treatment exposure based on the trial-reported time on treatment for the *BRCA1/2* population. |

Source: para 7.1, olaparib, Public Summary Document (PSD), November 2023 and compiled during the evaluation.

BRCA=breast cancer gene, ICER=incremental cost-effectiveness ration, m0HSPC=non-metastatic hormone sensitive prostate cancer mCRPC=metastatic castration-resistant prostate cancer, NHA=novel hormonal agent.

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

1. Requested listing

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | **Dispensed Price for Max. Qty** | **Max. qty packs** | **Max. qty units** | **№. of**  **Rpts** | **Available brands** |
| INITIAL TREATMENT:  OLAPARIB tablet, 150mg, 100mg, 56 | Published: $6,632.11a  Effective: $||||b | 2 | 112 | 2 | LYNPARZA®, AstraZeneca |
| CONTINUING TREATMENT:  OLAPARIB tablet, 150mg, 100mg, 56 | Published: $6,632.11a  Effective: $||||b | 2 | 112 | 5 | LYNPARZA®, AstraZeneca |

Blue shading represents information previously considered by the PBAC.

Source: Table 1-15, p57 of the resubmission.

Max, maximum; Qty, quantity, Rpts=repeats

1. Published AEMP $3,234.75 per 56 tablet pack; DMPQ $6,632.11 (2x56 tablet packs) based on current (July 2024) fees and mark ups
2. Effective AEMP $| | per 56 tablet pack; DMPQ $| | (2x56 tablet packs) based on current (July 2024) fees and mark ups.

|  |
| --- |
| **Category / Program:** General Schedule (Code GE) |
| **Prescriber type:** Dental Medical Practitioners Nurse practitioners Optometrists |
| **Severity: Metastatic** |
| **Condition:** Castration resistant metastatic carcinoma of the prostate |
| **Indication:** Castration resistant metastatic carcinoma of the prostate |
| **Treatment Phase: Initial** |
| **Restriction type:**  Authority Required (telephone/online PBS Authorities system) |
| **Clinical criteria:** |
| The condition must be associated with a class 4 or 5 *BRCA*1 or *BRCA*2 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:**  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 |
| **Administrative Advice:** Special Pricing Arrangements apply |

Blue shading represents information previously considered by the PBAC.

Source: Tables 1-17, 1-18; pp.61-62 of the resubmission.

* 1. The resubmission requested a Special Pricing Agreement (SPA), with the same published price as the November 2023 submission (AEMP = $3,234.75; DPMQ = $6,632.11 based on current fees and mark-ups) and the same effective price offered in the pre-PBAC response to the November 2023 submission (AEMP = $| |; DPMQ = $| | based on current fees and mark-ups). The proposed effective price was the same as the current effective price of olaparib monotherapy in patients with mCRPC following disease progression with an NHA. The resubmission acknowledged that the effective price may ultimately depend on the effective prices of talazoparib plus enzalutamide.
  2. The resubmission did not propose any change to the requested restriction compared to the November 2023 submission. The treatment criteria included a time provision to allow patients time to undertake *BRCA1/2* testing following diagnosis of mCRPC. Specifically, patients may initiate NHA monotherapy for mCRPC and switch to the olaparib plus abiraterone combination within 4 months following a positive *BRCA* test. The resubmission acknowledged that changes to the listing of abiraterone (and abiraterone plus methylprednisolone) may be required to (i) allow combination use with olaparib and (ii) allow treatment switching from enzalutamide to olaparib in combination with abiraterone (to provide patients choice of NHA prior to *BRCA* test results becoming available). Patients were proposed to continue treatment with olaparib plus abiraterone combination therapy until disease progression.

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

1. Population and disease
   1. Olaparib is a poly(adenosine diphosphate)-ribose polymerase inhibitor (PARPi). PARP enzymes are involved in DNA transcription, cell cycle regulation and DNA repair, and the anti-tumour effect of PARPi is dependent on an underlying defect in a cancer cell’s DNA damage response mechanisms.
   2. The proposed population, patients with mCRPC and *BRCA1/2* pathogenic variants, was the same as currently eligible for olaparib monotherapy on the PBS and previously described in the March 2021 and November 2021 olaparib submissions (paragraph 4.1, olaparib, Public Summary Document (PSD), November 2021). However, under the requested listing, olaparib in combination abiraterone would be positioned earlier in the treatment pathway than olaparib monotherapy, as an alternative first-line treatment option for NHA-naïve patients.

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

1. Comparator
   1. The resubmission nominated talazoparib plus enzalutamide as the main comparator, on the assumption that talazoparib and enzalutamide would proceed to PBS listing. The PBAC recommended PBS listing of talazoparib plus enzalutamide for the same indication at the July 2024 PBAC Meeting. The resubmission also nominated NHA monotherapy as a relevant secondary comparator, given talazoparib plus enzalutamide is not currently PBS listed.
   2. The ESC considered that the nominated comparators were appropriate.

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

1. Consideration of the evidence

Sponsor hearing

* 1. There was no hearing for this item.

Consumer comments

* 1. The PBAC noted and welcomed the input from individuals (6), health care professionals (1) and organisations (7) via the Consumer Comments facility on the PBS website. The PBAC noted that there were also comments received in November 2023 relating to the original submission. The comments from individuals and health professionals supported the olaparib resubmission and noted the benefits including improved survival and quality of life. The comments also noted the prohibitive cost of treatment if not subsidised.
  2. The Medical Oncology Group of Australia (MOGA) again expressed its strong support for the olaparib resubmission, 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]](#footnote-2), based on a comparison with placebo.
  3. The PBAC noted that Rare Cancers Australia expressed its support of the resubmission stating that this targeted therapy may be more effective for *BRCA1/2* patients.
  4. Inherited Cancers Australia (formerly Pink Hope) highlighted the benefits of having an additional targeted treatment option for patients with the BRCA1/2 pathogenic variant who are carrying an additional physical and psychological burden of disease through familial generations.
  5. The PBAC also noted the four inputs from the Prostate Cancer Foundation of Australia associated with this resubmission and 14 other consumer groups submissions associated with the November 2023 submission (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) Men’s 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 inputs 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

* 1. The resubmission presented updated clinical evidence compared to the November 2023 submission and re-organised the presentation of the clinical evidence given the change to the nominated comparators. The resubmission was based on two randomised trials comparing olaparib plus abiraterone versus abiraterone alone (PROpel, BRCAAWAY) and one randomised trial comparing talazoparib plus enzalutamide versus enzalutamide (TALAPRO-2). All three randomised trials were identified in the November 2023 submission; however, BRCAAWAY was previously excluded due to limited available data at that time. The resubmission also included additional recently published data from TALAPRO-2 Cohort 2, whereas only limited data from TALAPRO-2 Cohort 1 was included in the November 2023 submission.
  2. For comparison versus talazoparib plus enzalutamide, the resubmission conducted an indirect treatment comparison (ITC) based on evidence from PROpel and TALAPRO-2 assuming NHA alone as the common comparator. The resubmission noted that the PBAC had previously considered enzalutamide and abiraterone (i.e. the NHA common comparators) to be non-inferior in terms of comparative effectiveness (paragraph 7.6, enzalutamide PSD, July 2014 PBAC meeting). The resubmission also presented the results of a published (unanchored) matching-adjusted indirect comparison (MAIC), based on the evidence from PROpel and TALAPRO-2 trials (Castro et al, 2024).
  3. For comparison versus NHA monotherapy (abiraterone alone), the resubmission presented direct head-to-head evidence from PROpel and BRCAAWAY. The resubmission argued that BRCAAWAY, which allowed patients treated with abiraterone alone to cross over to olaparib monotherapy after disease progression, also provided evidence comparing combination treatment versus sequential treatment. At the November 2023 PBAC Meeting, the PBAC noted that no evidence was presented to suggest that the combination of olaparib and abiraterone was superior to sequential treatment of NHA monotherapy followed by olaparib monotherapy (paragraph 7.1, olaparib PSD, November 2023 PBAC Meeting).
  4. Details of the randomised trials presented in the resubmission are provided in Table 3. An independent search conducted during the evaluation identified additional data from BRCAAWAY (reported in Hussain 2024[c][[2]](#footnote-3)) and TALAPRO-2 Cohort 2 (reported in the March 2024 talazoparib PSD).

**Table 3: Trials and associated reports presented in the resubmission**

| **Study identifier (ID)** | **Reports** |
| --- | --- |
| **Olaparib\*** | |
| 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 |
| Fallah J, Xu J, Weinstock C et al. FDA approval summary: Olaparib in combination with abiraterone for treatment of patients with BRCA-mutated metastatic castration-resistant prostate cancer. *J Clin Oncol* 2023; 42: 605-613. |
| Saad F, Clarke NW, Oya M et al. Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpol): final prespecified overall survival results of a randomized, double-blind, phase 3 trial. *Lancet Oncol* 2023; 24: 1094-1108. |
| Saad F, Armstrong AJ, Oya M et al. Tolerability of Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: Further results from the phase 3 PROpel trial. *European Urology Oncology* 2024, article in press. |
| BRCAAWAY  NCT03012321 | Hussain M, Kocherginsky M, Agarwal N et al. BRCAAway: A randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) with DNA repair defects. *Genitourinary Cancer – Prostate, Testicular, and Penile* 2022. Poster 5018. |
| Hussain M, Kocherginsky M, Agarwal N et al. BRCAAway: A randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) bearing homologous recombination-repair mutations (HRRm). *Prostate Cancer – Advanced.* Meeting Abstract: 2024 ASCO Genitourinary Cancers Symposium. 2024(a). |
| Hussain M. ASCO GU 2024: BRCAAway: A randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with mCRPC bearing HRR mutations. *ASCO GU* 2024(b). |
| **Talazoparib\*** | |
| TALAPRO-2  NCT03395197 | Cohort 1 (all comers)  Agarwal N, Azad AA, Carles J 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; 402: 291-303. |
| Cohort 2 (HRR)  Fizazi K, Azad A, Matsubara N et al. First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: The phase 3 TALAPRO-2 trial. *Nature Medicine* 2024; 30: 257-264. |
| Both cohorts  Heiss BL, Chang E, Gao X et al. US Food and Drug Administration approval summary: Talazoparib in combination with enzalutamide for treatment of patients with homologous recombination repair gene-mutated metastatic castration-resistant prostate cancer. *Journal of Clinical* Oncology 2024; 42(15): 1851-1860. |

Blue shading represents information previously considered by the PBAC.

Source: Table 2-6 and Table 2-8, pp.80-87 of the resubmission.

\*Conference abstracts excluded from this table.

* 1. The key features of the included evidence are summarised in Table 4.

**Table 4: Key features of the included evidence**

| **Trial** | **N** | **Design/ duration** | **Risk of bias** | **Patient population** | **Outcome(s)** | **Use in modelled evaluation** |
| --- | --- | --- | --- | --- | --- | --- |
| **OLA+ABI vs. ABI** | | | | | | |
| PROpel | ITT (AC): 796  HRR sg: 226  *BRCA1/2* sg: 85 | R, DB, P3, MC ongoing | ITT: Low  HRR sg: High  *BRCA1/2* sg: High | 1L mCRPC  (± pathogenic variants) | OS, rPFS | ITT, HRR and *BRCA1/2* sg used to support CMA.  *BRCA1/2* sg was used in CUA. |
| BRCAAWAY | ITT (*BRCA1/2* ± ATM): 61c | R, OL, P2, MC, 3-armc, ongoing | ITT: High | 1L mCRPC  (*BRCA1/2* or ATM alterations) | PFS | Not used |
| **TAL+ENZ vs. ENZ** | | | | | | |
| TALAPRO-2 | Cohort 1 (AC): 805  Cohort 2 (HRRa): 399  *BRCA1/2* sg: 155 | R, DBb, P3, MC ongoing | Cohort 1: Low  Cohort 2: Low  *BRCA1/2* sg: High | 1L mCRPC  (± pathogenic variants) | OS, rPFS | ITT, HRR and *BRCA1/2* sg used to support CMA. |

Blue shading represents information previously considered by the PBAC.

Source: constructed during the evaluation.

ABI=abiraterone; AC=all-comers; ATM=ataxia telangiectasia mutated; BRCA=breast cancer gene; CMA=cost-minimisation analysis; CUA=cost-utility analysis; DB=double blind; ENZ=enzalutamide; HRR=homologous recombination repair; ITT=intention to treat; MC=multi-centre; mCRPC=metastatic castration-resistant prostate cancer; OL=open-label; OLA=olaparib; OS=overall survival; P2=phase 2; P3=phase 3; PFS=progression-free survival; R=randomised; rPFS=radiologic progression-free survival; sg=subgroup; TAL=talazoparib.

a Combined HRR population. 169 patients with HRR gene alteration from Cohort 1 plus an additional 230 patients selected for HRR gene alterations were recruited for a combined HRR-deficient population (n=399).

b TALAPRO-2: The sponsor, patients, and investigators were masked to TAL or PBO, while ENZ was open-label.

c BRCAAWAY was a three-arm trial, with patients randomised to ABI (n=19); OLA (n=21) and OLA+ABI (n=21).

* 1. PROpel, TALAPRO-2 and BRCAAWAY enrolled patients diagnosed with mCRPC despite background ADT, who were otherwise treatment-naïve in the mCRPC setting. Overall, the key eligibility criteria were similar across the trials, with the main exception being the criteria related to gene alternation status at baseline. PROpel enrolled genetically unselected all-comers and homologous recombination repair (HRR) status was assessed retrospectively; TALAPRO-2 prospectively tested HRR status at recruitment and enrolled genetically unselected all-comers in TALAPRO-2 Cohort 1, whereas only HRR positive patients were included in the TALAPRO-2 Cohort 2 (i.e. HRR positive); BRCAAWAY prospectively tested for gene status at recruitment and only enrolled patients with ATM, *BRCA1* or *BRCA2* pathogenic variants. There were other minor differences across the eligibility criteria in terms of life expectancy (≥6 months in PROpel and BRCAAWAY, ≥12 months in TALAPRO-2) and symptomatic disease (asymptomatic or mildly symptomatic in TALAPRO-2, asymptomatic or symptomatic in PROpel).
  2. There were some notable differences in baseline characteristics across the treatment arms in the *BRCA1/2* subgroup of PROpel, and the intention to treat (ITT) population of BRCAAWAY.
* In PROpel, patients with *BRCA1/2* pathogenic variants randomised to abiraterone monotherapy treatment group 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) compared to patients randomised to olaparib plus abiraterone. At the November 2023 PBAC Meeting, the PBAC noted that randomisation in PROpel was not stratified by *BRCA1/2* and the baseline characteristics across the two arms were not balanced. These factors may have biased results against abiraterone monotherapy, particularly given the small number of patients in each treatment group (paragraph 6.13, olaparib PSD, November 2023 PBAC Meeting).
* In BRCAAWAY, patients randomised to abiraterone monotherapy had a higher proportion of prior docetaxel treatment (42.1% versus 19.0%), worse ECOG performance status (ECOG 0/1: 52.6%/47.4% versus 76.2%/23.8%), and a lower proportion of patients with visceral metastases (10.5% versus 33.3%) compared to patients randomised to olaparib plus abiraterone. The resubmission acknowledged that variation in baseline disease between the arms of BRCAAWAY reflected in part the small sample size of the trial.
  1. The resubmission did not present a comparison of baseline characteristics for the *post-hoc* *BRCA1/2* subgroup in TALAPRO-2, but minor variations were noted at the March 2024 PBAC meeting in terms of ECOG status, Gleason score, median serum PSA, and prior anticancer therapies, including taxanes (paragraph 6.9, talazoparib PSD, March 2024 PBAC meeting). However, these differences did not appear to be important, given the PBAC considered that the *BRCA1/2* subgroup appeared reasonably well balanced with respect to potential confounders (paragraph 7.7, talazoparib PSD, March 2024 PBAC Meeting).

Comparative effectiveness

Comparison versus talazoparib plus enzalutamide

* 1. To compare olaparib plus abiraterone versus talazoparib plus enzalutamide across key clinical outcomes, the resubmission conducted a number of ITCs using the Bucher method, based on the evidence presented in PROpel and TALAPRO-2. The resubmission excluded the BRCAAWAY trial from the ITC due to the paucity of data and differences in patient characteristics, which had minimal impact on results. To improve interpretability of comparisons, the ITCs were conducted for three comparable populations enrolled in PROpel and TALAPRO-2: (i) all-comers (ii) HRR pathogenic variants and (iii) BRCA pathogenic variants.
  2. Table 5, Table 6 and Table 7 present the results of the ITCs for the three key outcomes of BICR-assessed rPFS, investigator assessed rPFS and OS, respectively.

**Table 5: ITC results for rPFS (BICR assessed) - olaparib plus abiraterone vs. talazoparib plus enzalutamide (PROpel and TALAPRO-2 trials)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **PROpel** | | **OLA+ABI**  **n/N (%)** | **PBO+ABI**  **n/N (%)** | **Absolute difference (% / months)** | **HR (95% CI)** |
| All-comer (ITT) DCO1~ | N events | 157/399 (39.3) | 218/397 (54.9) | 15.6 | **0.61 (0.49, 0.74)** |
| Median rPFS, months | 27.6 (19.6, NE) | 16.4 (13.8, 19.1) | 11.2 |
| All-comer (ITT) DCO2# | N events | 182/399 (45.6) | 242/397 (61.0) | 15.4 | **0.62 (0.51, 0.75)** |
| Median rPFS, months | 27.6 (20.5, 30.2) | 16.5 (13.8, 19.2) | 11.1 |
| HRR DCO1~ | N events | 43/111 (38.7) | 78/115 (67.8) | 29.1 | **0.45 (0.31, 0.65)** |
| Median rPFS, months | 28.75 | 13.77 | 15.0 |
| *BRCA* DCO1~a | N events | 12/47 (25.5) | 31/38 (81.6) | 56.1 | **0.18 (0.09, 0.34)** |
| Median rPFS, months | NE | 8.38 (4,16) | NE |
| **TALAPRO-2^** | | **TAL+ENZ**  **n/N (%)** | **PBO+ENZ**  **n/N (%)** | **Absolute difference (% / months)** | **HR (95% CI)** |
| All-comer (ITT Cohort 1b)  DCO 16 Aug 2022d | N events | 151/402 (37.6) | 191/403 (47.4) | 9.8 | **0.63 (0.51, 0.78)** |
| Median rPFS, months | NE (27.5, NE) | 21.9 (16.6, 25.1) | NE |
| HRR (ITT Cohort 2c)  DCO 3 Oct 2022e | N events | 66/200 (33.0) | 104/199 (52.3) | 19.3 | **0.45 (0.33, 0.61)** |
| Median rPFS, months | NE (21.9, NE) | 13.8 (11.0, 16.7) | NE |
| *BRCA* (Cohort 2)  DCO 3 Oct 2022e | N events | 15/71 (21.1) | 54/84 (64.3) | 43.2 | **0.20 (0.11, 0.36)** |
| Median rPFS, months | NE (NE, NE) | 11 (8.3, 11.1) | NE |
| **Indirect comparison: OLA+ABI vs TAL+ENZ** | | | | | |
| ITT (PROpel DCO1, TALAPRO-2 DCO 16 Aug 2022) | | | | | 0.968 (0.720, 1.302) |
| ITT (PROpel DCO2, TALAPRO-2 DCO 16 Aug 2022) | | | | | 0.984 (0.739, 1.311) |
| HRR | | | | | 1.0 (0.618, 1.618) |
| *BRCA* | | | | | 0.90 (0.369, 2.193) |

Blue shading represents information previously considered by the PBAC. **Bold** = statistically significant.

Source: Table 2-31, Table 2-62 to Table 2-64; pp.125, 171-175 of resubmission; Table 2 of Fallah 2023.

ABI=abiraterone; BICR=blinded independent central review; BRCA=breast cancer gene; CI=confidence interval; DCO=data cut-off; ENZ=enzalutamide; HR=hazard ratio; HRR=homologous recombination repair; ITT=intent-to-treat; NE=not estimable; OLA=olaparib; rPFS=radiographic progression-free survival; TAL=talazoparib.

^ primary outcome.

~ DCO1 PROpel (30 July 2021) median follow-up 19.3 months.

# DCO2 PROpel (14 March 2022) median duration of follow-up 24.9 months.

a Derived from Table 2-64, p175 of the resubmission (sourced from Attachment 2.7 of resubmission for DCO1). Table 2-64 stated that the median follow-up was 32.5 months (corresponding to that of DCO3) yet the numbers were those of DCO1 from Attachment 2.7 of resubmission.

b TALAPRO-2 genetically unselected all-comers. 805 patients with and without HRR gene alterations enrolled in Cohort 1 of TALAPRO-2.

c TALAPRO-2 Combined HRR population. 169 patients with HRR gene alteration from Cohort 1 plus an additional 230 patients selected for HRR gene alterations were recruited for a combined HRR-deficient population (n=399).

d DCO 16 Aug 2022 (Cohort 1), median follow-up 24.9 months.

e DCO 3 Oct 2022 (Cohort 2), median follow-up 17.5 months.

**Table 6: ITC results for rPFS (investigator assessed) - olaparib plus abiraterone vs. talazoparib plus enzalutamide (PROpel and TALAPRO-2 trials)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **PROpel ^** | | **OLA+ABI**  **n/N (%)** | **PBO+ABI**  **n/N (%)** | **Absolute difference** | **HR (95% CI)** |
| All-comer (ITT) DCO1~ | N events | 168/399 (42.1) | 226/397 (56.9) | 14.8 | **0.66 (0.54, 0.81)** |
| Median rPFS, months | 24.8 (20.5, 27.6) | 16.6 (13.9, 19.2) | 8.2 |
| All-comer (ITT) DCO2 | N events | 199/399 (49.9) | 258/397 (65.0) | 15.1 | **0.67 (0.56, 0.81)** |
| Median rPFS, months | 25.0 (NR, NR) | 16.4 (NR, NR) | 8.6 |
| All-comer (ITT) DCO3# | N events | 219/399 (54.9) | 277/397 (69.8) | 14.9 | **0.68 (0.57, 0.81)** |
| Median rPFS, months | 25.0 (20.6, 30.0) | 16.5 (13.9, 19.2) | 8.5 |
| HRR DCO1~ | N events | 43/111 (38.7) | 73/115 (63.5) | 24.8 | **0.50 (0.34, 0.73)** |
| Median rPFS, months | NE | 13.86 | NE |
| *BRCA* DCO1~a | N events | 14/47 (29.8) | 28/38 (73.7) | 43.9 | **0.23 (0.12, 0.43)** |
| Median rPFS, months | NE | 8.38 | NE |
| *BRCA* DCO3 | N events | 18/47 (38.3) | 31/38 (81.6) | 43.3 | **0.23 (0.12, 0.40)** |
| Median rPFS, months | 38.51 (23.66, NC) | 8.38 (5.52, 14.75) | 30.1 |
| **TALAPRO-2** | | **TAL+ENZ**  **n/N (%)** | **PBO+ENZ**  **n/N (%)** | **Absolute difference** | **HR (95% CI)** |
| All-comer (ITT Cohort 1b)  DCO 16 Aug 2022d | N events | 119/402 (29.6) | 153/403 (38.0) | 8.4 | **0.64 (0.50, 0.81)** |
| Median rPFS, months | NE (30.4, NE) | 30.3 (24.3, NE) | NE |
| HRR (ITT Cohort 2c)  DCO 3 Oct 2022e | N events | 52/200 (26.0) | 82/199 (41.2) | 15.2 | **0.48 (0.33, 0.67)** |
| Median rPFS, months | NE (30.3, NE) | 16.9 (13.9, 21.3) | NE |
| **Indirect comparison: OLA+ABI vs TAL+ENZ** | | | | | |
| ITT (PROpel DCO1, TALAPRO-2 DCO 16 Aug 2022) | | | | | 1.031 (0.753, 1.413) |
| ITT (PROpel DCO2, TALAPRO-2 DCO 16 Aug 2022 | | | | | 1.047 (0.773, 1.418) |
| ITT (PROpel DCO3, TALAPRO-2 DCO 16 Aug 2022) | | | | | 1.063 (0.788, 1.432) |
| HRR | | | | | 1.042 (0.619, 1.754) |

Blue shading represents information previously considered by the PBAC. **Bold** = statistically significant.

Source: Table 2-31, Table 2-62 to Table 2-64; pp.125, 171-175 of resubmission; Table 2 of Fallah 2023; Figure S1 of Agarwal 2023

ABI=abiraterone; BRCA=breast cancer gene; CI=confidence interval; DCO=data cut-off; ENZ= enzalutamide; HR=hazard ratio; HRR=homologous recombination repair; ITT=intent-to-treat; NA=not available; NE=not estimable; OLA=olaparib; rPFS=radiographic progression-free survival; TAL=talazoparib.

^ primary outcome

~ DCO1 PROpel (30 July 2021) median follow-up 19.3 months

# DCO3 PROpel (12 October 2022): median duration of follow-up 32.5 months.

a Derived from Table 2-64, p175 of the resubmission (sourced from Attachment 2.7 of resubmission for DCO1). Table 2-64 stated that the median follow-up was 32.5 months (corresponding to that of DCO3) yet the numbers were those of DCO1 from Attachment 2.7 of resubmission.

b TALAPRO-2 genetically unselected all-comers. 805 patients with and without HRR gene alterations enrolled in Cohort 1 of TALAPRO-2.

c TALAPRO-2 combined HRR population. 169 patients with HRR gene alteration from Cohort 1 plus an additional 230 patients selected for HRR gene alterations were recruited for a combined HRR-deficient population (n=399).

d DCO 16 Aug 2022 (Cohort 1), median follow-up 24.9 months.

e DCO 3 Oct 2022 (Cohort 2), median follow-up 17.5 months.

**Table 7: ITC results for OS - olaparib plus abiraterone vs. talazoparib plus enzalutamide (PROpel and TALAPRO-2 trials)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **PROpel** | | **OLA+ABI**  **n/N (%)** | **ABI**  **n/N (%)** | **Absolute difference** | **HR (95% CI)** |
| All-comer (ITT) DCO3 # | N events | 176/399 (44.1) | 205/397 (51.6) | 7.5 | 0.81 (0.67, 1.00) |
| Median OS, months | 42.05 (38.41, NE) | 34.69 (30.95, 39.29) | 7.4 |
| HRR DCO3 # | N events | 48/111 (43.2) | 69/115 (60.0) | 16.8 | **0.66 (0.45, 0.95)** |
| Median OS, months | NE | 28.45 | NE |
| *BRCA* DCO3 # | N events | 13/47 (27.7) | 25/38 (65.8) | 38.1 | **0.29 (0.14, 0.56)** |
| Median OS, months | NE | 22.97 (17.77, 34.17) | NE |
| **TALAPRO-2** | | **TAL+ENZ**  **n/N (%)** | **ENZ**  **n/N (%)** | **Absolute difference** | **HR (95% CI)** |
| All-comer (ITT Cohort 1a)  DCO 16 Aug 2022c | N events | 123/402 (30.6) | 129/403 (32.0) | 1.4 | 0.89 (0.69, 1.14) |
| Median OS, months | 36.4 (33.5, NE) | NE (33.7, NE) | NE |
| All-comer (ITT Cohort 1a)  DCO 3 Oct 2022 d | N events | 156/402 (38.8) f | 174/403 (43.2) f | 4.4 | 0.84 (0.67, 1.04) |
| Median OS, months | NE (37.3, NE) | 38.2 (34.1, 43.1) | NE |
| HRR (ITT Cohort 2b) DCO 3 Oct 2022 | N events | 43/200 (21.5) | 53/199 (26.6) | 5.1 | 0.69 (0.46, 1.03) |
| Median OS, months | NE (36.4, NE) | 33.7 (27.6, NE)) | NE |
| HRR (ITT Cohort 2b) DCO 28 Mar 2023 e | N events | 60/200 (30.0) | 76/199 (38.2) | 8.2 | **0.66 (0.47, 0.93)** |
| Median OS, months | 41.9 (34.5, NE) | 30.8 (26.8, 38.8) | NE |
| *BRCA* (Cohort 2b) DCO 3 Oct 2022 | N events | 13/71 (18.3)g | 21/84 (25.0)g | 6.7 | 0.61 (0.31,1.23) |
| Median OS, months | NE (29.8, NE)g | NE (24.5, NE)g | NE |
| *BRCA* (Cohort 2b) DCO 28 Mar 2023 e | N events | 18/71 (25.4) | 34/84 (40.5) | 15.1 | **0.47 (0.26, 0.85)** |
| Median OS, months | 41.9 (33, NE) | 26.1 (22.6, NE) | 15.8 |
| **Indirect comparison: OLA+ABI vs TAL+ENZ** | | | | | |
| ITT | | | | | 0.964 (0.716, 1.298) |
| HRR (TALAPRO-2 DCO 3 Oct 2022) | | | | | 0.957 (0.552, 1.657) |
| HRR (TALAPRO-2 DCO 28 Mar 2023) | | | | | 1.00 (0.603, 1.659) |
| *BRCA* (TALAPRO-2 DCO 3 Oct 2022) | | | | | 0.475 (0.179, 1.263) |
| *BRCA* (TALAPRO-2 DCO 28 Mar 2023) | | | | | 0.617 (0.248, 1.536) |

Blue shading represents information previously considered by the PBAC. **Bold** = statistically significant.

Source: Table 2-62 to Table 2-64; pp.171-175 of resubmission; PROpel CSR materials submitted with the resubmission; Table 2 of Fallah 2023; Figure S1 of Agarwal 2023; Table 2 and Table A3 of Heiss 2024.

ABI=abiraterone; BRCA=breast cancer gene; CI=confidence interval; DCO=data cut-off; ENZ=enzalutamide; HR=hazard ratio; HRR=homologous recombination repair; ITT=intent-to-treat; OLA=olaparib; OS=overall survival; rPFS=radiographic progression-free survival; TAL=talazoparib.

^ primary outcome

# DCO3 PROpel (12 October 2022): median duration of follow-up 32.5 months.

a TALAPRO-2 genetically unselected all-comers population. 805 patients with and without HRR gene alterations enrolled in Cohort 1 of TALAPRO-2.

b TALAPRO-2 combined HRR pathogenic variants population. 169 patients with HRR gene alteration from Cohort 1 plus an additional 230 patients selected for HRR gene alterations were recruited for a combined HRR-deficient population (n=399).

c TALAPRO-2 (Cohort 1) median duration of follow-up 24.9 months.

d Sourced from Table 2 of Heiss 2024.

e TALAPRO-2 DCO 28 March 2023. Data sourced from talazoparib PSD, March 2024 PBAC Meeting. Median duration of follow-up 27.6 months and 25.5 months in the TAL+ENZ and PBO+ENZ arms respectively (para 6.8, TAL PSD, March 2024 PBAC Meeting).

f The resubmission (Table 2-62, p172) erroneously reported results for patient numbers for DCO 16 Aug 2022 of TALAPRO-2 (sourced from Agarwal 2023) but reported the HR for DCO 3 Oct 2022 (sourced from Table 2 of Heiss 2024).

g These numbers were not reported in Table 2-64, p175 of the resubmission, but were sourced from talazoparib PSD, March 2024 PBAC Meeting.

* 1. Overall, the results of the ITCs showed no significant differences between olaparib plus abiraterone and talazoparib plus enzalutamide in any of the populations (all-comers, HRR, *BRCA*) in terms of rPFS (BICR-assessed), rPFS (investigator assessed) and OS.
  2. The estimated indirect hazard ratios for rPFS were all close to 1, given the magnitude of effect observed within each trial for rPFS (BICR and investigator) were highly similar (and statistically significant) in all populations. For example, at the latest data cuts available, both olaparib plus abiraterone and talazoparib plus enzalutamide showed similar reductions in the risk of rPFS (BICR) compared to placebo plus NHA in the all-comer population (38% and 39%, respectively), the HRR population (55% and 55%, respectively) and the BRCA population (82% and 80%, respectively).
  3. Similarly, the estimated indirect hazard ratios for OS were close to 1 given the magnitude of the effect observed within each trial for OS was similar, with the exception being in the *BRCA1/2* subgroup that numerically favoured olaparib plus abiraterone. For example, at the latest data cuts, both olaparib plus abiraterone and talazoparib plus enzalutamide showed no difference in OS for the all-comer population compared to placebo plus NHA, but a significant reduction in risk of death in the HRR population (34% and 34%, respectively) and the *BRCA1/2* population (71% and 53%, respectively). The ESC noted that the numerically larger treatment effect observed in the *BRCA1/2* subgroup of PROpel may be due to an imbalance of prognostic factors across the treatment arms related to survival.
  4. Figure 1 presents the results of the MAIC reported by Castro et al 2024, comparing olaparib plus abiraterone versus talazoparib plus enzalutamide in terms of rPFS and OS in patients with HRR and *BRCA1/2* pathogenic variants. The analysis used individual patient data from TALAPRO-2 Cohort 2 (DCO 3 October 2022) and published summary data from PROpel (DCO1 30 July 2021 for rPFS; DCO3 12 October 2022 for OS), adjusted for key stratification factors (prior taxane chemotherapy in castration sensitive prostate cancer) and other prognostic factors identified in the literature (visceral metastasis; bone only metastasis; ECOG score; PSA levels and Gleason score).

Figure 1: KM curves of rPFS and OS results for TAL+ ENZ (purple) and OLA+ABI (orange) from the MAIC in Castro et al. (2024)

|  |  |
| --- | --- |
| **[A] rPFS HRR (n=150 TAL+ENZ; n=111 OLA+ABI)**  HR = 0.668 (0.429, 1.041)\* | **[B] rPFS BRCA (n=60 TAL+ENZ; n=47 OLA+ABI)**  HR = 0.824 (0.349, 1.944)\* |
| **Figure 1: KM curves of rPFS and OS results for TAL+ ENZ (purple) and OLA+ABI (orange) from the MAIC in Castro et al. (2024) [A] rPFS HRR (n=150 TAL+ENZ; n=111 OLA+ABI) HR = 0.668 (0.429, 1.041)*** | **Figure 1: KM curves of rPFS and OS results for TAL+ ENZ (purple) and OLA+ABI (orange) from the MAIC in Castro et al. (2024) [B] rPFS BRCA (n=60 TAL+ENZ; n=47 OLA+ABI) HR = 0.824 (0.349, 1.944)*** |
| **[C] OS HRR (n=150 TAL+ENZ; n=111 OLA+ABI)**  HR = 0.663 (0.406, 1.082)\* | **[D] OS BRCA (n=60 TAL+ENZ; n=47 OLA+ABI)**  HR=1.014 (0.406, 2.530)\* |
| **Figure 1: KM curves of rPFS and OS results for TAL+ ENZ (purple) and OLA+ABI (orange) from the MAIC in Castro et al. (2024) [C] OS HRR (n=150 TAL+ENZ; n=111 OLA+ABI) HR = 0.663 (0.406, 1.082)*** | **Figure 1: KM curves of rPFS and OS results for TAL+ ENZ (purple) and OLA+ABI (orange) from the MAIC in Castro et al. (2024) [D] OS BRCA (n=60 TAL+ENZ; n=47 OLA+ABI) HR=1.014 (0.406, 2.530)*** |

Source: Figures 1A, 2A, 1C and 2C of Castro et al. 2024

ABI=abiraterone; *BRCA*=breast cancer gene; ENZ=enzalutamide; HR=hazard ratio; HRR=homologous recombination repair; OLA=olaparib; OS=overall survival; rPFS=radiographic progression-free survival; TAL=talazoparib.

\* These results from the Castro et al 2024[[3]](#footnote-4) conference poster differs slightly from results presented in the conference abstract.

* 1. Overall, the MAIC by Castro et al 2024 found no statistically significant difference between olaparib plus abiraterone versus talazoparib plus enzalutamide in terms of rPFS or OS for patients with HRR or *BRCA1/2* pathogenic variants. The ESC noted that there was a relatively large (47%) reduction in the effective sample size of the TALAPRO-2 Cohort 2 population after reweighting in the *BRCA1/2* subgroup, highlighting the differences in the two populations at baseline and potentially limiting the applicability of the results. The analysis was also limited by the available baseline data reported in both trials and hence likely did not control for all prognostic factors (such as time to mCRPC from continuous ADT).
  2. At the March 2024 PBAC Meeting, the PBAC considered the results of a similar MAIC in the all-comer population, based on individual patient data from TALAPRO-2 Cohort 1 and published summary data from PROpel, adjusted for prognostic factors. *BRCA1/2* status was not ranked as a key prognostic factor but was considered in an exploratory analysis. The results suggested superiority of talazoparib plus enzalutamide versus olaparib plus abiraterone in an all-comer population, in terms of rPFS (HR = 0.73; 95% CI: 0.56, 0.93) but not OS (HR = 0.85; 95% CI: 0.67, 1.08). This analysis, however, was considered highly uncertain and not robust for decision making (paragraphs 6.33 to 6.37, talazoparib PSD, March 2024).

Comparison versus NHA monotherapy (i.e. abiraterone monotherapy)

* 1. Table 8 presents the key clinical outcomes of rPFS/PFS and OS reported in the most comparable populations of PROpel (HRR and *BRCA1/2* subgroups) and BRCAAWAY (ITT – ATM or *BRCA1/2*), comparing olaparib plus abiraterone versus abiraterone monotherapy.

Table 8: Summary of PFS and OS reported in PROpel and BRCAAWAY trials

| **Trial, outcome and population** | | **n/N (%)** | | **Median rPFS or OS (95% CI), months** | | **HR (95% CI)** |
| --- | --- | --- | --- | --- | --- | --- |
| **OLA+ABI** | **ABI** | **OLA+ABI** | **ABI** |
| **PROpel** | **rPFS (BICR assessed), DCO1: 30 July 2021b** | | | | | |
| HRR | 43/111 (38.7) | 78/115 (67.8) | 28.75 | 13.77 | **0.45 (0.31, 0.65)** |
| *BRCA1/2* | 12/47 (25.5) | 31/38 (81.6) | NE | 8.38 (NE, NE) | **0.18 (0.09, 0.34)** |
| **rPFS (investigator assessed), DCO1: 30 July 2021b** | | | | | |
| HRR | 43/111 (38.7) | 73/115 (63.5) | NE | 13.86 | **0.50 (0.34, 0.73)** |
| *BRCA1/2* | 14/47 (29.8) | 28/38 (73.7) | NE | 8.38 (NR, NR) | **0.23 (0.12, 0.43)** |
| **rPFS (investigator assessed), DCO3: 12 October 2022**d | | | | | |
| *BRCA1/2* | 18/47 (38.3) | 31/38 (81.6) | 38.51 (23.66, NC) | 8.38 (5.52, 14.75) | **0.23 (0.12, 0.40)** |
| **OS, DCO3: 12 October 2022d** | | | | | |
| HRR | 48/111 (43.2) | 69/115 (60.0) | NE | 28.45 | **0.66 (0.45, 0.95)** |
| *BRCA1/2* | 13/47 (27.7) | 25/38 (65.8) | NE | 22.97 (NR, NR) | **0.29 (0.14, 0.56)** |
| **BRCAAWAY** | **PFSa, DCO: NRe** | | | | | |
| *BRCA1/2* or ATM – ASCO GU (Hussaing 2024(b) | NR | NR | 39 (22, NR) | 8.4 (2.9, 17) | **0.28 (0.13, 0.65)** |
| **PFSa, DCO: 5 January 2024**f | | | | | |
| *BRCA1/2* or ATM Hussain 2024(c) | 11/21g (52.4) | 15/19g (78.9) | 39 | 8.6 | **0.33 (0.15, 0.72)** |
| **OSe, DCO 5 January 2024** | | | | | |
| *BRCA1/2* or ATM | 0/21 (0) | 3/19 (15.8) | NR | NR | NR |

Blue shading represents information previously considered by the PBAC. **Bold** = statistically significant

Source: pp.124-132 of resubmission

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.

a Defined as disease progression as per RECIST 1.1, PCWG3 criteria, clinical assessment i.e., disease-related symptoms that in the opinion of the physician require intervention), or death (sourced from Hussain 2024(c)).

b DCO1 PROpel (30 July 2021) minimum follow-up 13 months.

d DCO3 PROpel (12 October 2022): median duration of follow-up 32.5 months.

e BRCAAWAY median duration of follow-up among patients alive: 16 months (ABI arm); 23 months (OLA+ABI arm).

f BRCAAWAY median follow-up time from randomisation until last encounter among randomised patients still alive was 18 months (Hussain 2024(c)).

g BRCAAWAY: progressions were radiographic progressions with the exception of 2 patients in the ABI arm and 1 patient in the OLA+ABI arm which were PSA progressions.

* 1. The BRCAAWAY trial reported a statistically significant improvement in PFS for patients randomised to olaparib plus abiraterone compared to abiraterone monotherapy. The resubmission stated that the PFS in BRCAAWAY was consistent with the rPFS (investigator-assessed) in PROpel (DCO 3), with nearly identical median PFS or rPFS (i.e. approximately 39.0 months and 8.4 months for olaparib plus abiraterone and abiraterone monotherapy respectively). The results in both trials should be interpreted with caution given the small sample sizes (BRCAAWAY n=40 in the relevant comparison arms; PROpel n=85 in the *BRCA1/2* subgroup). At the November 2023 PBAC Meeting, the PBAC considered that, although the rPFS and OS results favoured olaparib plus abiraterone for patients with a *BRCA1/2* pathogenic variant, the magnitude of the clinical effect was highly uncertain (paragraph 7.8, olaparib PSD, November 2023 PBAC Meeting).
  2. The resubmission also argued that the results of BRCCAWAY provided evidence that the combination treatment of olaparib plus abiraterone (for first line mCRPC) provided substantially greater gains in PFS compared to sequential treatment of abiraterone monotherapy (for first line mCRPC) followed by olaparib monotherapy (for 2L mCRPC). At progression, 8 of the 19 patients randomised to the abiraterone arm (i.e. following 15 PFS events) crossed over to olaparib, with a median time from randomisation to progression on crossover treatment (i.e. PFS2) of 16 months (95% CI: 7.8, 25). In comparison, the median time from randomisation to progression (i.e. PFS) for olaparib plus abiraterone was 39.0 months, indicating a substantial improvement in PFS compared to sequential treatment. The ESC, noting the small sample size in BRCCAWAY (n = 40) and that 8/19 abiraterone patients crossed over to receive olaparib, considered that the trial was not sufficiently powered to compare combination and sequential treatment.

Comparative harms

* 1. To compare safety outcomes between olaparib plus abiraterone versus talazoparib plus enzalutamide, the resubmission presented an extensive series of ITCs using the Bucher method, based on the all-comer (i.e., ITT) populations in PROpel (DCO 3, approx. 33 months median follow-up) and TALAPRO-2 Cohort 1 (DCO 16 August 2022, approx. 25 months median follow-up). Safety data reported in BRCAAWAY was not included in the ITCs but was consistent with the safety data reported in PROpel.
  2. Table 9 summarises adverse events outcomes in PROpel (all-comer/ITT) and TALAPRO-2 Cohort 1 (all-comer/ITT), including common AEs and Grade ≥3 AEs found to differ between the two PARPi plus NHA treatments in the ITCs.

Table 9: Summary of key adverse events in PROpel and TALAPRO-2

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **PROpel (all-comer/ITT)** | | **TALAPRO-2 (Cohort 1)** | |
| **AE category** | **OLA+ABI n/N (%)** | **PBO+ABI n/N (%)** | **TAL+ENZ n/N (%)** | **PBO+ENZ n/N (%)** |
| Any AE | 389/398 (97.7) | 380/396 (96.0) | 392/398 (98.5) | 379/401 (94.5) |
| Any TEAE | 316/398 (79.4) | 227/396 (57.3) | 357/398 (89.7) | 279/401 (69.6) |
| Any AE of Grade ≥3 (treatment-related)\*^ | 106/398 (26.7) | 39/396 (9.8) | 234/398 (58.8) | 71/401 (17.7) |
| Any SAE | 161/398 (40.5) | 126/396 (31.8) | 157/398 (39.4) | 107/401 (26.7) |
| Any AE leading to death | 26/398 (6.5) | 20/396 (5.1) | 13a/398 (3.3) | 18a/401 (4.5) |
| AE leading to discontinuationb, n (%) | 71/398 (17.8) | 43/396 (10.9) | NR | NR |
| Discontinued PARPi/PBO due to AE | 69/398 (17.3) | 34/396 (8.6) | 75/398 (18.8) | 49/401 (12.2) |
| Dose reduction of PARPi/PBO due to AE\* | 112/398 (28.1) | 56/396 (14.1) | 210/398 (52.8) | 27/401 (6.7) |
| Dose interruption of PARPi/PBO due to AE\* | 206/398 (51.8) | 128/396 (32.3) | 247/398 (62.1) | 84/401 (20.9) |
| **Common AEs (any Grade)** | | | | |
| Anaemia\*^ | 197/398 (49.5) | 69/396 (17.4) | 262/398 (65.8) | 70/401 (17.5) |
| Nausea\*\*^ | 122/398 (30.7) | 57/396 (14.4) | 82/398 (20.6) | 50/401 (12.5) |
| Diarrhoea\*\* | 82/398 (20.6) | 42/396 (10.6) | 57/398 (14.3) | 55/401 (13.7) |
| Neutropenia\*^ | 21/398 (5.3) | 4/396 (1.0) | 142/398 (35.7) | 28/401 (7.0) |
| Leukopenia\*^ | 12/398 (3.0) | 2/396 (0.5) | 88/398 (22.1) | 18/401 (4.5) |
| Thrombocytopenia\* | 27/398 (6.8) | 17/396 (4.3) | 98/398 (24.6) | 14/401 (3.5) |
| **AEs of Grade ≥3** | | | | |
| Anaemia\* | 64/398 (16.1) | 13/396 (3.3) | 185/398 (46.5) | 17/401 (4.2) |
| Back pain\*^ | 4/398 (1.0) | 6/396 (1.5) | 10/398 (2.5) | 4/401 (1.0) |
| Neutropenia\*^ | 5/398 (1.3) | 1/396 (0.3) | 73/398 (18.3) | 6/401 (1.5) |
| Leukopenia\*^ | 3/398 (0.8) | 0/396 (0) | 25/398 (6.3) | 0/401 (0) |
| Thrombocytopenia\*^ | 3/398 (0.8) | 2/396 (0.5) | 29/398 (7.3) | 4/401 (1.0) |
| Lymphopenia\*^ | 6/398 (1.5) | 4/396 (1.0) | 20/398 (5.0) | 4/401 (1.0) |

Blue shading represents information previously considered by the PBAC.

Source: Table 2-65 to Table 2-67 pp.177-179 of resubmission, Table 3 of Agarwal 2023.

ABI=abiraterone; AE=adverse event; ENZ=enzalutamide; OLA=olaparib; PARPi=poly-ADP ribose polymerase inhibitor; PBO=placebo; TAL=talazoparib; TEAE=treatment-related adverse events.

a Assumed in the resubmission to be equivalent to Grade 5 event. However, the number of patients with Grade 5 events appear to be higher than the number of treatment-related deaths reported in Agarwal et al 2023: treatment-related deaths occurred in 0 and 2 patients in the TAL+ENX and ENZ groups, respectively.

b Participants who have an AE record that indicates that the AE caused the participants to be discontinued from the study.

\* Indirect treatment comparison (OLA+ABI vs TAL+ENZ) statistically significant based on risk difference: OLA+ABI superior to TAL+ENZ

\*\* Indirect treatment comparison (OLA+ABI vs TAL+ENZ) statistically significant based on risk difference: OLA+ABI inferior to TAL+ENZ.

^ Statistically significant using risk difference statistic but not significant using relative risk statistic.

* 1. The safety data in PROpel indicated that, compared to placebo plus abiraterone, patients treated with olaparib plus abiraterone experienced significantly higher number of Grade ≥ 3AEs, treatment-related AEs, serious AEs, and AEs leading to discontinuation, dose reduction or dose interruption. Similarly, the safety data in TALAPRO-2 Cohort 1 indicated that, compared to placebo plus enzalutamide, patients treated with talazoparib plus enzalutamide experienced significantly higher number of any AEs, serious adverse events, Grade ≥3 AEs and more AEs leading to discontinuation of study treatment, dose interruption and dose reductions.
  2. Based on ITCs and the risk difference statistic only, the resubmission concluded that patients treated with talazoparib plus enzalutamide compared to olaparib plus abiraterone, were significantly more likely to experience Grade ≥ 3 AEs and AEs leading to dose reduction. In particular, patients treated with talazoparib plus enzalutamide were significantly more likely to experience anaemia (any Grade and Grade ≥ 3), haematologic abnormalities of any Grade (neutropenia, thrombocytopenia, leukopenia), and Grade ≥ 3 haematologic abnormalities (neutropenia, thrombocytopenia, leukopenia and lymphopenia). In contrast, patients treated with olaparib plus abiraterone experienced a significantly higher risk of gastrointestinal AEs (nausea and diarrhoea).
  3. Overall, the results of the safety data indicate that treatment with PARPi plus NHA was associated with clinically significant toxicities compared to NHA monotherapy. However, it was unclear whether the ITCs presented in the resubmission would provide a sufficiently reliable approach for assessing the comparative safety profiles of the two PARPi plus NHA treatment regimens as:
* The findings of the ITCs across safety outcomes were dependent on the risk statistic assumed for the analysis. Most of the statistically significant findings based on the risk difference statistic were not statistically significant based on the relative risk statistic. Based on both the risk difference and relative risk, patients treated with talazoparib plus enzalutamide were more likely to experience anaemia (Grade ≥ 3) and thrombocytopenia of any grade, whereas patients treated with olaparib plus abiraterone were more likely to experience diarrhoea.
* There were differences in the follow-up periods in PROpel and TALAPRO-2, which were not controlled for, and the resubmission presented a very large number of comparisons which increases the chances of finding significant differences by chance. In this case, the resubmission conducted over forty indirect comparisons, hence even if the risk of adverse events were identical for the two treatments, we would expect at least two of the comparisons to be significantly different due to chance alone.
* It was unclear whether the comparative safety profile of the two treatment regimens in the all-comer populations would be sufficiently representative of patients with *BRCA1/2* pathogenic variants, given there would likely be differences in average treatment exposure that may influence safety outcomes. For example, compared to the ITT population in PROpel, the mean treatment exposure to olaparib plus abiraterone was higher in the *BRCA1/2* subgroup (743-762 days versus 613-647 days) and mean treatment exposure to abiraterone monotherapy was lower in the *BRCA1/2* subgroup (393 days versus 565 days).
  1. The Pre-Sub-Committee Response (PSCR) acknowledged the uncertainties with regards to the ITC for safety outcomes, stating that the ITC was reliant on a comparison between the all-comer populations from both the PROpel and TALAPRO-2 studies given the lack of available safety data for the *BRCA1/2* subgroup from the TALAPRO-2 trial. However, given the larger sample sizes and longer duration of follow-up for the all-comer populations, this was considered appropriate and more representative of the overall safety profiles for each combination therapy. Nevertheless, given the limitations of the ITCs raised in the evaluation, notably the differences in treatment exposures across trials and subpopulations, as well as the large number of tests conducted, the PSCR recognised that the magnitude of the differences observed may be uncertain.

Benefits/harms

* 1. For comparison to talazoparib plus enzalutamide, a benefits and harms table is not presented as the resubmission made a claim of non-inferior effectiveness and the indirect treatment comparison for safety outcomes did not allow for a reliable comparison between the two PARPi plus NHA treatments in patients with mCRPC and *BRCA1/2* pathogenic variants.
  2. For comparison to abiraterone alone, a benefits and harms table is not presented as no rPFS or OS data were presented at specific time points and the resubmission did not present safety outcomes for the *BRCA1/2* subgroup of PROpel.
  3. However, on the basis of direct evidence from PROpel in the all-comer population, for every 100 patients treated with olaparib plus abiraterone in comparison to abiraterone, after a median follow-up of approximately 33 months:
* Approximately 22 additional patients would have treatment-related adverse events, 17 additional patients would have Grade ≥ 3 treatment-related adverse events and 9 additional patients would have serious adverse events.
* Approximately 32 additional patients would have anaemia (all grades), 13 additional patients would have Grade ≥ 3 anaemia, 16 additional patients would have nausea (all grades), and 10 additional patients would have diarrhoea (all grades.

Clinical claim

* 1. The resubmission described olaparib plus abiraterone as:
* superior in terms of effectiveness and inferior in terms of safety compared to NHA monotherapy (i.e., abiraterone monotherapy); and
* non-inferior in terms of effectiveness and superior in terms of safety compared to talazoparib plus enzalutamide. Acknowledging the uncertainties associated with the ITCS for the safety outcomes presented, the PSCR revised the superior safety claim, stating that a claim of non-inferior safety may be more appropriate.
  1. The ESC considered that the clinical claims versus NHA monotherapy were adequately supported by the totality of the evidence presented in the resubmission including the all-comer and HRR subgroup data of PROpel, but the magnitude of the clinical effectiveness in the *BRCA1/2* subgroup remained uncertain. Although the new clinical evidence in BRCAAWAY (for patients with ARM or *BRCA1/2*) was generally consistent with the *BRCA1/2* subgroup data in PROpel in terms of rPFS, the ESC considered that the results of BRCAAWAY were uncertain due to small sample size and unbalanced prognostic factors at baseline.
  2. The PBAC considered that the claims of superior comparative effectiveness and inferior comparative safety compared to NHA monotherapy in the *BRCA1/2* subgroup were reasonable. The PBAC considered that the magnitude of effectiveness remained uncertain.
  3. The ESC considered that the clinical claims versus talazoparib plus enzalutamide were also adequately supported by the totality of the evidence in terms of non-inferior effectiveness. The ESC also considered that the revised claim of non-inferior safety was reasonable. The ESC noted that olaparib and talazoparib had differing safety profiles, but the rates of discontinuation were similar for both (17.3% of PROpel patients discontinued olaparib and 18.8% of TALAPRO-2 patients discontinued talazoparib).
  4. The PBAC considered that the claims of non-inferior comparative efficacy and non-inferior comparative safety compared to talazoparib plus enzalutamide were reasonable.

Economic analysis

* 1. The resubmission presented two economic evaluations:
* For comparison versus talazoparib plus enzalutamide, a cost-minimisation approach (CMA) based on the clinical claim of non-inferior efficacy and superior safety.
* For comparison versus NHA monotherapy, an updated cost-utility analysis (CUA) based on a superior efficacy and inferior safety claim. The CUA aimed to address concerns raised by the PBAC at the November 2023 PBAC Meeting.

Cost-minimisation approach (versus talazoparib plus enzalutamide)

* 1. Table 10 summarises the key components and assumptions of the CMA. The resubmission assumed equivalent total costs for treatment with olaparib plus abiraterone versus talazoparib plus enzalutamide over 957 days of treatment, accounting for cost-offsets associated with fewer cases of grade ≥3 anaemia with olaparib plus abiraterone. The PSCR removed the cost offsets from the CMA.
  2. To undertake the analysis, the resubmission estimated the effective AEMP for (i) talazoparib, assuming a | |% rebate applied to the requested published price for breast cancer (paragraph 2.1, talazoparib PSD, November 2019) and (ii) enzalutamide, derived from the known effective price for abiraterone (minus methylprednisolone), excluding the 5% statutory price reduction applied to abiraterone in April 2024 and adjusting for the number of capsules per pack (28).

Table 10. Key components and assumptions of the cost-minimisation approach presented in the resubmission

|  |  |
| --- | --- |
| **Component** | **Claim or assumption** |
| **Therapeutic claim: effectiveness** | Non-inferior, based on an ITC which used the clinical evidences from *BRCA1/2* subgroups of PROpel and TALAPRO-2 (Cohort 2) trials and showed non-inferior effectiveness of OLA+ABI vs TAL+ENZ |
| **Therapeutic claim: safety** | Superior, based on an ITC which used the clinical evidences from the all-comers population (non BRCA-specific) of PROpel and TALAPRO-2 trials and showed superior safety of OLA+ABI vs TAL+ENZ. The clinical claim was revised to non-inferior in the PSCR. |
| **Evidence base** | Indirect treatment comparison of ITT, HRR and *BRCA1/2* subgroups (for efficacy) and the ITT (for safety) of PROpel and TALAPRO-2 trials. |
| **Equi-effective doses a** | Equi-effective doses per trial protocol and respective PI were:   * OLA: 300 mg (two 150 mg tablets) twice daily, equivalent to 600 mg daily * ABI: 1000 mg (four 250 mg tablets) once daily plus 5 mg prednisolone twice daily a * TAL: 0.5 mg capsule once daily * ENZ: 160 mg (four 40 mg capsules) as a single oral daily dose |
| Relative dose intensities (from PROpel, ITT): OLA and TAL: 91.7%, ABI and ENZ: 96.3% b |
| Treatment durations (from PROpel, *BRCA1/2* subgroup): 957 days in both combination therapies c |
| **Direct medicine costs** | * TAL effective price was estimated using the published ex-manufacturer price for the breast cancer indication (para 2.1, Talazoparib PSD, November 2019), assuming a |% rebate on the published price. It was assumed that flat pricing existed across the different doses of TAL. * The price per pack of TAL was slightly higher than for OLA reflecting the different pack sizes (30 and 28 days, respectively) resulting in a slightly higher fees, mark-ups and co-pays for OLA compared to TAL. * ABI price was derived from the Yonsa Mpred price (no SPA, including the corticosteroid component) * ENZ price was estimated using the abiraterone AEMP (Yonsa Mpred minus prednisolone) prior to the 5% anniversary price cut in April 2024, adjusted for the number of capsules per pack (×28). |
| **Other costs or cost offsets** | The incremental costs for managing Grade ≥3 anaemia, sourced from the ITC based on data from the ITT populations of the TALAPRO-2 Cohort 1 and PROpel trials (RD = 0.29). These costs were removed from the CMA in the PSCR. |

Source: Table 3-1, p200, Table 3-2, p201, Table 3-8, p205, and Table 3.12- p210 of the resubmission.

ABI=abiraterone, AE=adverse event, *BRCA*=breast cancer gene, ENZ=enzalutamide, ITC=indirect treatment comparison, ITT=intention to treat, OLA=Olaparib, PI=product information, PSD=public summary document, RD=risk difference, SPA=special pricing arrangement, SPR=statutory price reduction, TAL=talazoparib.

1. While the Yonsa Mpred abiraterone formulation was not used in the clinical trial, this was considered by the PBAC to be bioequivalent to the original abiraterone formulation and is currently available on the PBS in the mCRPC setting. The equi-effective dose is 500mg abiraterone (four 125mg tablets) once daily plus 4mg methylprednisolone twice daily.
2. If a patient experiences a grade ≥3 toxicity or an intolerable adverse reaction with enzalutamide, the recommendation is to withhold dosing for one week or until symptoms improve to grade ≤2, then resume at the same or a reduced dose (120 mg or 80 mg) if warranted. For the purpose of the model dose reductions were considered by applying a relative dose intensity.
3. Both combination therapies are intended to be used until treatment progression. As such, the equi-effective dose considered the duration of treatment, in addition to dose intensities.
   1. The equi-effective doses were estimated based on the trial doses, which were consistent with the recommended doses in the respective product information:

* Olaparib 300 mg (two 150 mg tablets) twice daily, plus abiraterone:
  + Originator formulation (Zytiga®): abiraterone 1000 mg (four 250 mg tablets) once daily in combination with 5 mg prednisone or prednisolone twice daily;
  + Fine particle formulation (Yonsa Mpred®): abiraterone 500 mg (four 125 mg tablets) once daily in combination with 4 mg methylprednisolone twice daily.

The PBAC has previously considered Yonsa Mpred® 500 mg to be bioequivalent to Zytiga® 1000 mg (para 1.2, abiraterone and methylprednisolone, PSD, November 2022).

* Talazoparib 0.5 mg (one 0.5 mg capsule) once daily plus enzalutamide 160 mg (four 40 mg capsules) once daily.
  1. As both PARPi plus NHA treatment regimens continue until disease progression, including dose reductions/interruptions due to AEs and renal impairment, the CMA included parameters for both treatment duration and relative dose intensity (RDI). However, in the absence of comparative evidence, the resubmission assumed average treatment duration and average dose intensity would be equal for both PARPi plus NHA regimens. These parameters were estimated from the median time on treatment (957 days, for the *BRCA1/2* subgroup) and mean dose intensity (91.7% for PARPi and 96.3% for NHA, for the ITT population) reported in PROpel.
  2. The CMA presented in the submission included the incremental cost of managing Grade ≥ 3 anaemia as a cost-offset for olaparib plus abiraterone. The resubmission estimated for every 100 patients treated with a PARPi plus NHA treatment, an additional 29.4 patients would experience Grade ≥3 anaemia with talazoparib plus enzalutamide compared to olaparib plus abiraterone, based on the results of the ITC on safety outcomes. The resubmission estimated the cost of treating severe anaemia at $3,414 per event, based on the cost of RBCs from the National Blood Authority (NBA) Australia’s National Product List (whole blood unit: $375.0 × 8.86 units) and the cost of administering a blood transfusion from the MBS (item: 13706, $91.7). These cost offsets were removed in the PSCR.
  3. Table 11 presents the results of the CMA based on estimated effective prices.

Table 11. Results of the cost-minimisation approach presented in the resubmission

| **Treatment** | **OLA plus ABI** | | **TAL plus ENZ** | | **Sources** |
| --- | --- | --- | --- | --- | --- |
| **Drug** | **OLA** | **ABI** | **TAL** | **ENZ** | **Respective components** |
| **Treatment duration and dosing** | | | | | |
| Daily dose (mg) | 600 | 1000 | 0.5 | 160 | Respective PIs |
| Relative dose Intensity | 91.7% | 96.3% | 91.7% | 96.3% | mean RDI from PROpel trial |
| Dose received per day (mg) | 550 | 963 | 0.46 | 154 | Calculated |
| Treatment duration (days) | 957 | 957 | 957 | 957 | PROpel *BRCA1/2* subgroup |
| Cumulative dose over duration of treatment (mg) | 526,541 | 921,591 | 438.78 | 147,455 | Calculated |
| Tablet / capsule strength (mg) | 150 | 250 | 0.5 | 40 | Respective PIs |
| Pack size | 56 | 120 | 30 | 112 | Respective PIs |
| Number of packs required for total treatment duration | 62.7 a | 30.7 | 29.3 | 32.9 | Calculated |
| **Pricing** | | | | | |
| Published AEMP per pack | $3,234.75 | $1,171.61 | $7,307.23 | $3,316.45 | TAL PSD Nov 2019, PBS items: 11522K, 10174L, 2698B |
| Assumed rebates | |　% | |　% | |　% | |　% | Assumptions |
| Effective AEMP per pack | **$||** | $　| | $　| | $　| | Calculated |
| Effective AEMP per 28/30 day supply | **$||** | $　| | $　| | $　| | Calculated |
| **Cost-minimisation results for assumed effective ex-manufacturer prices** | | | | | |
| Drug costs per patient | $　| | $　| | $　| | $　| | Calculated |
| Total drug cost per patient | $| | | $| | | Calculated |
| Incremental cost of Grade≥3 anaemia | - | | $| | | Calculated using ITC-reported RD (29.45%) |
| Total treatment costs per patient | **$|** | | **$|** | | Calculated |
| **Revised CMA – no cost offsets associated with the cost of Grade≥3 anaemia** | | | | | |
| Total treatment costs per patient | **$|** | | **$|** | | Calculated |
| Effective AEMP per pack | **$||** | $　| | $　| | $　| | Calculated |
| Effective AEMP per 28/30 day supply | **$||** | $　| | $　| | $　| | Calculated |
| Effective cost per day | **$||** | $　| | $　| | $　| | Calculated |

Source: Tables 3-13, pp210-211 of the resubmission and compiled during the evaluation.

ABI=abiraterone, AEMP=approved ex-manufacturer price, ENZ=enzalutamide, ITC=indirect treatment comparison, OLA=Olaparib, PBS=pharmaceutical benefit scheme, PSD=public summary document, RD=risk difference, TAL=talazoparib.

1. The resubmission contained a minor error in calculating the number of olaparib packs needed for the total treatment duration. However, this error does not affect the final calculations.
   1. The total cost per patient per course was estimated to be $||| ||| for olaparib plus abiraterone and talazoparib plus enzalutamide. This resulted in an AEMP for olaparib of $| | per pack or $| | per 28-day supply. Excluding the anaemia-related incremental costs, as agreed to in the PSCR, reduced the proposed AEMP of olaparib by | |% to $| | per pack (or $| | per 28-day supply). For the PARPi component of the combination regimens, the average daily cost for olaparib in the PSCR revised CMA (AEMP = $| | per day) was slightly higher than talazoparib (AEMP = $| | per day) due to the | |% cost difference between abiraterone (AEMP = $| | per day) and enzalutamide (AEMP = $| | per day); assuming the same NHA costs (based on the cost of abiraterone) reduces the proposed AEMP for olaparib by | |% to $| | ($| | per 28-day supply).
   2. The proposed small price advantage for olaparib over talazoparib, on a component basis, may not be justified. It may not be reasonable for one component of a combination regimen to achieve a price advantage over the corresponding component of a comparator combination regimen due to price differences in the other included components, and particularly for equi-effective components. In this case, abiraterone and enzalutamide were listed on a cost-minimisation basis with non-inferior efficacy and safety, and the current 5% price difference between the two treatments is only due to timing – where abiraterone recently underwent a 10-year 5% statutory price reduction and the same price reduction will apply to enzalutamide in the near future. The PSCR stated that the prices applied in the CMA reflected prices at the time of submission and noted that these prices were consistently applied in the cost-effectiveness analysis for talazoparib plus enzalutamide, and the CUA presented in this resubmission. The PSCR stated that statutory price reductions (SPRs) are a part of the F1 medicines life cycle on the PBS and pricing differences due to the different timings of the SPRs are common among medicines that have been listed on a cost-minimisation basis. While the evaluator considered that this would put olaparib at a small price advantage, the PSCR noted that olaparib has already taken its 5-year SPR and will see its 10-year anniversary price cut for olaparib in 2027 ahead of the 5-year SPR for talazoparib in 2030. This will result in a temporary 3-year price advantage for talazoparib. The pre-PBAC response reiterated that current prices should be used to inform the CMA.

Cost-utility analysis (versus NHA monotherapy)

* 1. Table 12 presents a summary of key changes to the CUA presented in the resubmission, compared to the November 2023 submission and November 2023 pre-PBAC response. Overall, the model remained largely unchanged from the 2023 pre-PBAC response with the exception of a few minor parameter updates (progressed disease health state utility and some resource unit prices).

Table 12. Summary of key changes to the cost-utility analysis

| **Component** | **November 2023 submission** | **November 2023 submission; pre-PBAC response** | **November 2024 resubmission** | **Impact of change (vs. Nov. 23 submission)** |
| --- | --- | --- | --- | --- |
| **Price** | $|||| | Reduced to $||||. This represented a ||||% reduction in the price. | Unchanged from the pre-PBAC response. | High  (reverting to Nov. 2023 proposed price increased the ICER by 15%) |
| **Time horizon** | 15 years  The PBAC considered a 15-year time horizon was too long given the poor prognosis of patients with *BRCA1/2* pathogenic 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 (Para 7.10, olaparib PSD, November 2023). | Reduced to 10 years | Unchanged from the pre-PBAC response.  The PSCR accepted a 7.5 year time horizon. | Moderate  (reverting to a 15-year time horizon would decrease the ICER by 10%) |
| **Extrapolation of PFS / OS** | rPFS in both arms: log-normal;  OS in the intervention arm: exponential;  OS in the control arm: log logistic.  The PBAC considered that the extrapolations, which resulted in 20% of patients in the olaparib and abiraterone arm remaining alive at 15 years, were not clinically plausible (Para 7.10, olaparib PSD, November 2023). The ESC considered that there should be a convergence of the OS curves (Para 6.60, olaparib PSD, November 2023). | rPFS in both arms: Weibull;  OS in both arms: Weibull.  Compared to the main body of the November 2023 submission, the Weibull extrapolations resulted in fewer olaparib patients alive at 10 years (35% to 26%). | Extrapolation functions were unchanged from the pre-PBAC response.  The resubmission modelled convergence of OS from 5 years in a sensitivity analysis only. | Low  (reverting to Nov. 2023 selected extrapolation functions increased the ICER by 1%) |
| **Time on treatment** | ToT in both arms: Exponential  The estimated time on treatment was uncertain due to (i) unknown source, (ii) the extrapolations exceeded PFS, (iii) extrapolations based on visual fit, and (iv) poor external validation against PBS use of NHAs (Para 6.67, olaparib PSD, November 2023). The mean duration of treatment for NHA monotherapy in the model 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. 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 responses to NHAs (Para 6.79, olaparib PSD, November 2023). | ToT in both arms: Weibull  Resulted in shorter mean duration of treatment in both arms (ABI ToT reduced from 14 to 13 months; OLA+ABI ToT reduced from 41 to 37 months). The model included a restriction that prevented ToT from exceeding PFS | ToT extrapolated curves were unchanged from the pre-PBAC response.  The resubmission did not provide the corresponding Kaplan-Meier data, but reported the mean treatment exposure in the *BRCA1/2* pathogenic variants subgroup of PROpel at censoring (DCO3 - SAF): approx. 24 months for OLA+ABI and approx. 13 months for ABI (Table 2-49, p159 of the resubmission). | Low  (reverting ToTs to Exponential functions increased the ICER by 1%) |
| **Utilities** | PF = 0.816  PD = 0.778  The PBAC considered that the 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 (Para 7.10, olaparib PSD, November 2023). | Unchanged. | PF = 0.816  PD = 0.726  The revised health state utility for PD was based on the pre-progressed utility from the PROfound trial. | Low  (reverting to PROpel utility for PD state decreased the ICER by 1%) |

Blue shading indicates data previously seen by the PBAC.

Source: Table 3-14, p213 of the resubmission and compiled during the evaluation.

AEMP=Approved Ex Manufacturer Price, *BRCA*=breast cancer gene, ICER=incremental cost effectiveness ratio, NHA=novel hormonal agent, PD= progressed disease, PF=progression-free, QALY=quality adjusted life years.

* 1. Figure 2 presents extrapolation functions for OS, rPFS and ToT assumed in resubmission (same as the November 2023 pre-PBAC response) compared to the November 2023 submission, indicated as the ‘current base’ and ‘previous base’ cases, respectively. Though the ESC previously advised that convergence of OS over a 7.5-year time horizon would be necessary due to the poor prognosis of *BRCA1/2* patients (paragraph 6.60, olaparib PSD, November 2023), the resubmission did not apply any convergence factor in the revised base case over a 10-year time horizon. To address any remaining uncertainties associated with 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 in PROpel and to align with the March 2024 talazoparib model, the PSCR reduced the time horizon to 7.5 years in the base case.
  2. The PSCR maintained that convergence of the OS curves over a 7.5 year time horizon was not appropriate. The PSCR noted that (i) Kaplan-Meier data for patients treated with olaparib and abiraterone show that 28.6% of deaths had occurred at 41 months (3.4 years; average 8.4% deaths per year) and (ii) converging OS curves at 7.5 years resulted in a dramatic linear decline in survival (rate of death = 17.0% per year) that was highly unlikely clinically given the observed OS in the trial and given that 15% of patients are expected not to have progressed at 7.5 years. The PSCR did note that converging the OS curves at 10 years resulted in a more clinically plausible decline in survival over time with an estimated 71% of deaths occurring over 6.6 years (average death rate of 10.7% per year).

Figure 2. Extrapolation for the olaparib plus abiraterone and NHA arms of the model

|  |  |
| --- | --- |
| OS | Figure 2. Extrapolation for the olaparib plus abiraterone and NHA arms of the model OS |
| **rPFS** | Figure 2. Extrapolation for the olaparib plus abiraterone and NHA arms of the model rPFS |
| **ToT** | Figure 2. Extrapolation for the olaparib plus abiraterone and NHA arms of the model ToT |

Source: Compiled during the evaluation

ABI=abiraterone, KM=Kaplan-Meier, NHA=novel hormonal agent, OLA=olaparib, OS=overall survival; PF=progression free, rPFS=radiographic progression free survival; ToT=time on treatment.

Note: The ‘previous base’ case refers to the November 2023 submission, while the ‘current base’ case refers to the extrapolation functions applied in the pre-PBAC response and the November 2024 resubmission.

* 1. Overall, the change in extrapolations functions - from exponential and loglogistic to Weibull functions for OS, from lognormal to Weibull functions for rPFS, and from exponential to Weibull functions for ToT - had minimal effect on the ICER. Although the Weibull functions corresponded to lower absolute estimates of PFS, OS and ToT in both of the treatment arms compared to the November 2023 submission, the incremental differences in PFS, OS and ToT between the treatment arms were similar. The ESC noted that the OS extrapolations resulted in approximately 40% of patients in the olaparib plus abiraterone arm remaining alive at 7.5 years, approximately 25% alive at 10 years and approximate 10% alive at 15 years compared to 0% of patients in the abiraterone arm at all time points. The ESC considered that the OS extrapolation applied to the olaparib plus abiraterone arm lacked clinical plausibility, particularly considering the poor prognosis for patients with *BRCA1/2* mCRPC.
  2. Key drivers of the model are described in Table 13.

Table 13. Key drivers of the model

| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| OS benefit | The resubmission extrapolated rPFS and OS KM data from the *BRCA1/2* subgroup. 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, favors olaparib plus abiraterone |
| Time horizon | The resubmission used a 10-year time horizon. However, given the uncertainty surrounding the OS data and previous PBAC recommendations, a shorter time-horizon may be more appropriate. | High, favors olaparib plus abiraterone |

Blue shading indicates data previously seen by the PBAC.

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

* 1. Table 14 summarises the results of the stepped analysis presented in the resubmission (over 10 years) compared to the November 2023 submission (over 15 years).

Table 14. Results of the stepped economic evaluation showing model changes

|  | **November 2023 submission (over 15 years)** | | | **Resubmission (current, over 10 years)** | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Step and component** | **OLA+ABI** | **NHA monotherapy** | **Increment** | **OLA+ABI** | **NHA monotherapy** | **Increment** |
| **Step 1: cost per LY – 36-month time horizon** | | | | | | |
| Costs | $　| | $52,580 | $| | $　| | $51,738 | $　| |
| LYG | 2.440 | 1.907 | 0.533 | 2.440 | 1.906 | 0.533 |
| Incremental cost/extra LY gained | | | $|1 |  | | $　|　2 |
| **Step 2: cost per LY- 15-year time horizon in Nov. 2023 submission and 10-year time horizon in resubmission** | | | | | | |
| Costs | $　| | $63,221 | $| | $　| | $62,244 | $　| |
| LYG | 5.870 | 2.397 | 3.474 | 4.888 | 2.139 | 2.748 |
| Incremental cost/extra LY gained | | | $|3 |  | | $　|　3 |
| **Step 3: cost per QALY – 15-year time horizon in Nov. 2023 submission and 10-year time horizon in resubmission** | | | | | | |
| Costs | $　| | $63,221 | $| | $　| | $62,244 | $　| |
| QALY | 4.667 | 1.873 | 2.794 | 3.799 | 1.619 | 2.180 |
| **Incremental cost/extra QALY gained** | | | **$　|　4** |  | | **$　|　 4a** |
| **November 2024 PSCR revised evaluation** | | | | | | |
| **Step 3: cost per QALY – 7.5-year time horizon** | | | | | | |
| Costs | - | - | - | $　| | $62,178 | $　| |
| QALY | - | - | - | 3.408 | 1.618 | 1.790 |
| **Incremental cost/extra QALY gained** | | | **-** |  | | **$　|　4** |

Blue shading indicates data previously seen by the PBAC.

Source: Table 3-26, p149 of the November 2023 submission and Table 3-42, p254 of the resubmission.

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

1. To confirm the reported changes, the ICER from the November 2023 submission was recalculated by reverting the parameters to those used in the previous submission. This recalculation yielded an ICER nearly identical to the one reported in the first submission, with <0.1% difference.

*The redacted values correspond to the following ranges:*

*1 $155,000 to < $255,000*

*2 $135,000 to < $155,000*

*3 $45,000 to < $55,000*

*4 $55,000 to < $75,000*

* 1. The revised ICER presented in the resubmission ($55,000 to < $75,000 per QALY) was nearly identical to the base case ICER presented in the November 2023 submission ($55,000 to < $75,000 per QALY). The effects of the olaparib price reduction offered in the November 2023 pre-PBAC response was largely offset by the effects of the reduction in time horizon from 15 to 10 years, also implemented in the November 2023 pre-PBAC response. The switch to Weibull extrapolation functions and other updated parameters (restricting ToT to PFS, lower health state utility for progressing disease and other minor changes to resource unit costs) had minimal effect of the ICER. When the time horizon was reduced to 7.5 years in the PSCR, the ICER increased to $55,000 to < $75,000 per QALY. The ESC considered that the incremental QALY gains of 2.18 after 10 years and 1.79 after 7.5 years were overestimated and were a reflection of the clinically implausible extrapolation of OS in the olaparib plus enzalutamide arm.
  2. Table 15 illustrates the step-by-step impact on the ICER of incorporating the parameter changes from the November 2023 submission (reduced olaparib price, reduced time horizon, change to extrapolation functions, lower health state utility for progressive disease, and the updated olaparib price), which were implemented over time in the November 2023 PSCR, November 2023 PBAC response and the resubmission.

Table 15. Results of the stepped economic evaluation showing model changes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Parameter change, incremental** | **Incr Cost** | **Incr QALYs** | **ICER**  **(incr % change vs Nov. 23 ICER)** |
| **November 2023 submission base case** | **Presented by the sponsor** | **$||** | **2.794** | **|**1 |
| **November 2023 submission PSCR revised base case** | + ToT cannot exceed rPFS | $　| | 2.79 | ||1 (+|||%) |
| **Presented by the sponsor** | **NR** | **NR** | **|**1 **a (+||%)** |
| **November 2023 pre-PBAC response base case** | + Price: AEMP $|||| | $　| | 2.79 | ||2(-||%) |
| + time horizon: 10 years | $　| | 2.24 | ||1 (+|||%) |
| + Weibull extrapolations (rPFS, OS, ToT) | $　| | 2.21 | ||1 (+|||%) |
| **Presented by the sponsor** | **NR** | **NR** | **|**1 **a (+||%)** |
| **November 2024 resubmission base case** | + PD health state utility | $　| | 2.18 | ||1 (+|||%) |
| + Updated unit prices b | $　| | 2.18 | ||1 (+|||%) |
| **Presented by the sponsor** | **$||** | **2.18** | **|**1 **(+　|　%)** |
| **November 2024 resubmission PSCR** | + time horizon: 7.5 years | **$||** | **1.79** | **|**1 **(+　|　%)** |

Blue shading indicates data previously seen by the PBAC.

Source: compiled during the evaluation

Incr=incremental, QALY=quality adjusted life years

Note: Step-wise changes were applied to the cost-effectiveness Excel model from the November 2023 submission. Minor discrepancies were identified between the calculated ICERs during the evaluation and those reported by the PSCR, pre-PBAC response, and the resubmission, though the source of these differences was unclear.

1. The model was not presented; therefore, the ICER cannot be verified.
2. This included minor DPMQ updates to the comparator arms, as well as the subsequent treatment prices. Olaparib (2L, similar to the proposed 1L): from $| | to $| |. Abiraterone: from $| | for ABI + $| | for MPred to $| | for ABI+MPred combination. Enzalutamide: from $| | to $| |. Cabazitaxel: from a public DPMQ of $| | and a private DPMQ of $| | to new public and private DPMQs of $| | and $| |. Docetaxel: from a public DPMQ of $| | and a private DPMQ of $| | to new public and private DPMQs of $| | and $| |.

*The redacted values correspond to the following ranges:*

*1 $55,000 to < $75,000*

*2 $45,000 to < $55,000*

***Drug cost/patient/course: $|||||||| (assuming a treatment duration of 957 days)***

* 1. Table 16 outlines the drug cost per patient for olaparib plus abiraterone and both comparator arms, talazoparib plus enzalutamide and NHA monotherapy, across the economic models and the financial estimates. Costs are based on the proposed price of olaparib, the actual price of abiraterone and the assumed AEMPs of talazoparib and enzalutamide.

Table 16. Drug cost per patient (*BRCA1/2* subgroup) for proposed and comparator drugs

|  | **Trial** | **Model** | **Financial estimates** | **Trial** | **Model** | **Financial estimates** |
| --- | --- | --- | --- | --- | --- | --- |
| **Comparison versus talazoparib plus enzalutamide (CMA)** | | | | | | |
|  | **OLA+ABI** | | | **TAL+ENZ** | | |
| Mean dose (mg/dose) | OLA: 600, ABI:1000, Pred:10 | | | TAL: 0.5, ENZ: 160 | | |
| Treatment duration (days) a | OLA: 957 ABI: 960 | 957 | | NR | 957 | |
| Cost/patient/course b, c | NR | OLA: $　|　  ABI: $　|　,  **Total: $||** | OLA: $||,  ABI: $　|　,  **Total: $||** | NR | TAL: $||, ENZ: $37,779, **Total: $　|**d | TAL: $||,  ENZ: $41,802,  **Total: $||** |
| **Comparison versus abiraterone (CUA)** | | | | | | |
|  | **OLA+ABI** | | | **NHA monotherapy** | | |
| Mean dose (mg/dose) | OLA: 600, ABI:1000, Pred: 10 | | | ABI:1000, Pred:10, ENZ:160 | | |
| Treatment duration (days) a | OLA: 957 ABI: 960 | Median: 913  (Mean: 1,133) e | 957 | 300 | Median: 243 (Mean: 395) e | 300 |
| Cost/patient/course c | NR | OLA: $　|　  ABI: $　|　  **Total: $　|** e | OLA: $||  ABI: $|||  **Total: $　|** | NR | $16,976 f | ABI: $12,476  ENZ: $13,104  **Mean: $12,871** f |

Blue shading indicates data previously seen by the PBAC.

Source: Table 2-49, p159, Table 3-2, p201, Table 3-6, p204, Table 3-8, p205, Table 3-13, pp210-1, Table 3-41, p253 of the resubmission and compiled during the evaluation

ABI=abiraterone, BRCA=breast cancer gene, cc=concomitant therapies, CMA=cost-minimisation analysis, CUA=cost-utility analysis, ENZ=enzalutamide, Mpred=methylprednisolone, NR=not reported, NHA=novel hormonal agents, OLA=olaparib, Pred=prednisolone, RDI=relative dose intensity, ToT=time on treatment.

Note 1: Values were rounded up.

Note 2: Costs were reported at the DPMQ level, except for the CMA costs, which were reported at the AEMP level.

1. The resubmission used the PROpel trial-reported median treatment durations (i.e., 957 days for PARPi+NHA and 300 days for NHAs) in the CMA and both financial estimates. In the *BRCA1/2* subgroup of the PROpel trial, the mean treatment durations were 743 days for OLA, 763 days for ABI in combination, and 394 days for NHA monotherapy. The economic model reported mean times on treatment as 1,133 days for OLA+ABI and 395 days for NHA monotherapy.
2. This was estimated by applying RDIs from the ITT population of PROpel (91.7% for olaparib and talazoparib, and 96.3% for abiraterone and enzalutamide), and based on a 957-day median ToT in the *BRCA1/2* subgroup of PROpel. Costs are reported in AEMP level for the CMA and DPMQ level for the financial estimations.
3. Abiraterone cost was estimated based on the effective price of Yonsa Mpred (PBS:13263), which includes methylprednisolone.
4. This was derived from the CMA calculation in the talazoparib plus enzalutamide arm, excluding the incremental costs associated with managing Grade ≥3 anaemia.
5. Reported from the half-cycle corrected and undiscounted values from the economic model of the resubmission (Attachment 3.2).
6. The resubmission assumed that 37% of patients would take abiraterone, and 63% would take enzalutamide.
   1. The cost per patient per treatment course estimated in the CMA and financial analysis was calculated based on the mean dose (accounting for relative dose intensity) and median treatment duration reported in the *BRCA1/2* subgroup of the PROpel trial. Whereas the cost per patients per treatment course estimated in the CUA was calculated based on the mean dose and mean treatment duration in the *BRCA1/2* subgroup. Other small differences were largely due to the use of AEMP in the CMA and the use of the DPMQ in the CUA and financial estimates.

Estimated PBS usage & financial implications

* 1. This resubmission was not considered by DUSC.
  2. The resubmission presented updated financial estimates under two financial impact models:
* The first model assumed talazoparib plus enzalutamide was listed on the PBS. This scenario estimated the incremental cost of listing olaparib plus abiraterone using a mixed epidemiological and market-share approach.
* The second model assumed talazoparib plus enzalutamide was not listed on the PBS. This scenario was considered in the November 2023 submission and estimated the incremental cost of listing olaparib plus abiraterone versus NHA monotherapy as the standard of care scenario, using an epidemiological approach.
  1. Both scenarios used the same epidemiological approach to determine the number of mCRPC patients with *BRCA1/2* mutations who would be eligible for treatment. Only incident patients were included in the eligible population, as it was expected that patients would commence treatment shortly after their mCRPC diagnosis.
  2. Table 17 summarises the parameters and data sources applied in the financial analysis to calculate the initiating patient population.

Table 17. Data sources and parameter values used to estimate the initiating patient population

| **Data** | **November 2023 submission** | **November 2023 pre-PBAC response** | **Resubmission** | **Source** | **Comment** |
| --- | --- | --- | --- | --- | --- |
| **Eligible patients** | | | | | | |
| Incident patients  (based on total NHA initiations in 1L mCRPC) | Yr 1: 2024   |  |  | | --- | --- | | Y1 | ||||1 | | Y2 | ||||1 | | Y3 | ||||1 | | Y4 | ||||1 | | Y5 | ||||2 | | Y6 | ||||2 | | Unchanged | Yr 1: 2025   |  |  | | --- | --- | | Y1 | ||||1 | | Y2 | ||||1 | | Y3 | ||||1 | | Y4 | ||||2 | | Y5 | ||||2 | | Y6 | ||||2 | | Estimated using NHA initiations 2016-2020 from 10% PBS sample with average annual growth rate (6.86%) applied based on 2016-2019 figures (Table 16, olaparib, PBAC Minutes, November 2021). | As reported in the olaparib PSD (Table 16), the average growth rate also excluded 2020 from the calculations as COVID-19 was assumed to have impacted initiations, but the 2020 value was used to predict future years. It might be more appropriate to estimate what 2020 numbers should have been and carried those through. |
| NHA-naïve mCRPC patients | |  |  |  | | --- | --- | --- | | Yr | %^ | N | | 1 | 52% | ||||1 | | 2 | 47% | ||||1 | | 3 | 43% | ||||1 | | 4 | 43% | ||||1 | | 5 | 43% | ||||1 | | 6 | 43% | ||||1 |   ^ % of incident patients, progressed from m0HSPC, mHSPC & m0CRPC | |  |  |  | | --- | --- | --- | | Yr | %^ | N | | 1 | 52% | ||||1 | | 2 | 47% | ||||1 | | 3 | 43% | ||||1 | | 4 | 41% | ||||1 | | 5 | 39% | ||||1 | | 6 | 38% | ||||1 |   ^ % of incident patients, progressed from m0HSPC, mHSPC & m0CRPC | |  |  |  | | --- | --- | --- | | Yr | %^ | N | | 1 | 25% | ||||1 | | 2 | 25% | ||||1 | | 3 | 25% | ||||1 | | 4 | 25% | ||||1 | | 5 | 25% | ||||1 | | 6 | 25% | ||||1 |   ^ % of incident patients, progressed from m0HSPC | NHA-naïve patients were estimated in two steps: i) proportion of patients who progressed to mCRPC ii) the proportion of NHA-naïve population. | The resubmission updated the NHA-naïve population by excluding patients who had progressed from mHSPC and m0CRPC stages, as these stages may involve potential NHA initiation. It only included patients who had progressed from the m0HSPC stage (representing 25% of the population, based on an average of shares reported in Svensson 2021[[4]](#footnote-5) [23%] and Verry 2022[[5]](#footnote-6) [27%]) and assumed all (100%) of these patients were NHA-naïve. |
| *BRCA1/2* positive, NHA-naïve, mCRPC patients (Eligible) | |  |  | | --- | --- | | Yr | N | | 1 | ||||3 | | 2 | ||||3 | | 3 | ||||3 | | 4 | ||||3 | | 5 | ||||3 | | 6 | ||||3 | | |  |  | | --- | --- | | Yr | N | | 1 | ||||3 | | 2 | ||||3 | | 3 | ||||3 | | 4 | ||||3 | | 5 | ||||3 | | 6 | ||||3 | | |  |  | | --- | --- | | Yr | N | | 1 | ||||3 | | 2 | ||||3 | | 3 | ||||3 | | 4 | ||||3 | | 5 | ||||3 | | 6 | ||||3 | | 90% *BRCA* test uptake and 7% prevalence rates were sourced from the olaparib PSD (para 4.4, olaparib, PSD, Nov. 2021). | *BRCA* test uptake and prevalence rates remained unchanged and were appropriate. |
| **Treatment utilisation (PARPi + NHA)** | | | | | | |
| Uptake rate of PARPi + NHA | Yr 1-6: ||||% | Unchanged | Unchanged | Assumption: ||||% uptake for PARPi + NHA combination therapy. | ||||% uptake rate for the PARPi+NHA combination therapy in NHA-naïve BRCA//2 positive 1L-mCRPC population was considered reasonable. |
| Market share of OLA + ABI (TAL+ENZ SoC) | OLA+ABI: ||||% of the PARPi+NHA market  Yr 1-6: ||||% (||||%×||||%) | Not presented. | Presented for the first time. TAL+ENZ was the SoC. | Among patients initiating PARPi + NHA, ||||% were expected to prefer OLA+ABI over TAL+ENZ, resulting in an overall uptake rate of ||||%. | The ||||% uptake rate of OLA+ABI compared to TAL+ENZ might have been overestimated, primarily due to safety concerns associated with the use of corticosteroids alongside abiraterone. |
| Number initiating & continuing treatment | |  |  | | --- | --- | | Yr | N (PARPi + NHA) | | 1 | ||||3 | | 2 | ||||3 | | 3 | ||||3 | | 4 | ||||3 | | 5 | ||||3 | | 6 | ||||3 | | |  |  | | --- | --- | | Yr | N (PARPi + NHA) | | 1 | ||||3 | | 2 | ||||3 | | 3 | ||||3 | | 4 | ||||3 | | 5 | ||||3 | | 6 | ||||3 | | |  |  | | --- | --- | | Yr | N (PARPi + NHA) | | 1 | ||||3 | | 2 | ||||3 | | 3 | ||||3 | | 4 | ||||3 | | 5 | ||||3 | | 6 | ||||3 | | Calculated using the ||||% uptake for PARPi+NHA and 100% continuation rates. No grandfathered or prevalent patients were included. | A 100% treatment continuation was justified because discontinuations were already accounted for in the ToT data. |

Blue shading indicates data previously seen by the PBAC.

Source: Table 4-1, p263, Table 4-2, p265, Table 4-4, p267, Table 4-8, p273, Table 4-9, p273 of the resubmission and compiled during the evaluation.

ABI=abiraterone, BRCA=breast cancer gene, ENZ=enzalutamide, m0CRPC=non-metastatic castrate resistant prostate cancer, m0HSPC=non-metastatic hormone sensitive prostate cancer, mCRPC=metastatic castrate resistant prostate cancer, mHSPC=metastatic hormone sensitive prostate cancer, NHA=novel hormonal agent, OLA=olaparib, PARPi=poly- PBS=Pharmaceutical Benefits Scheme.

*The redacted values correspond to the following ranges:*

*1 500 to < 5,000*

*2 5,000 to < 10,000*

*3 < 500*

Financial implications (versus talazoparib plus enzalutamide as the SoC)

* 1. Table 18 presents the estimated use and financial impact of olaparib plus abiraterone, when talazoparib plus enzalutamide is the SoC. The financial estimates used the proposed/estimated effective AEMPs/DPMQs, consistent with the economic analysis.

Table 18. Estimated use and financial implications (SoC= talazoparib plus enzalutamide, Year 1=2025)

|  | **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 | |　2 | |　2 | |　2 | |　3 |
| NHA-naïve patients | |　1 | |　1 | |　1 | |　1 | |　1 | |　1 | |　2 |
| *BRCA1/2*-positive patients, eligible for PARPi+NHA | |　4 | |　4 | |　4 | |　4 | |　4 | |　4 | |　4 |
| Number of patients treated with OLA + ABI | |　4 | |　4 | |　4 | |　4 | |　4 | |　4 | |　4 |
| Number of OLA + ABI scripts dispensed | |　1 | |　1 | |　1 | |　1 | |　1 | |　1 | |　5 |
| Number of TAL + ENZ scripts decreased | -||1 | -||1 | -||1 | -||1 | -||1 | -||1 | -　|　5 |
| **Estimated financial implications of olaparib plus abiraterone** | | | | | | | |
| **Net cost of OLA+ABI to PBS/RPBS** | **||||6** | **||||6** | **||||6** | **||||6** | **||||6** | **||||6** | **||||7** |
| **Estimation changes in financial impact of currently listed treatments** | | | | | | |  |
| Cost offsets for TAL+ENZ | |　8 | |　8 | |　8 | |　8 | |　8 | |　8 | |　8 |
| **Net financial implications** | | | | | | |  |
| **Net cost to PBS/RPBS** | **||6** | **||6** | **||6** | **||6** | **||6** | **||6** | **|　6** |
| Net cost to MBS | |　**6** | |　**6** | |　**6** | |　**6** | |　**6** | |　**6** | |　**6** |
| Net change to health budget | |　**6** | |　**6** | |　**6** | |　**6** | |　**6** | |　**6** | |　**6** |

Source: Table 4-11, p274, Tables 4-14 and 4-15, p276, Table 4-21, p279, Tables 4-22, 4-23, p280, Table 4-24, p281 and Table 4-38, p278 of the resubmission, and compiled during the evaluation

ABI=abiraterone, BRCA=breast cancer gene 1, ENZ=enzalutamide, m0CRPC=non-metastatic castrate resistant prostate cancer, 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, TAL=talazoparib.

Note: The financial estimates use effective prices for olaparib and assumed effective prices for talazoparib, abiraterone and enzalutamide.

*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 < 500*

*5 10,000 to < 20,000*

*6 $0 to < $10 million*

*7 $30 million to < $40 million*

*8* *net cost saving*

* 1. The resubmission estimated a net cost to PBS/RPBS of approximately $0 to < $10 million over the first six years of listing for olaparib plus abiraterone combination therapy in first line treatment of mCRPC, when talazoparib plus enzalutamide is the standard of care scenario.
  2. The minimal cost associated with the potential listing of olaparib was due to different pack sizes (one olaparib prescription supplies 28 days of treatment, whereas one talazoparib prescription supplied 30 days of treatment). The estimated utilisation of PARPi plus NHA treatments, for the purposes of revising any potential risk sharing arrangement, were still subject to some uncertainty (refer to Financial implications versus NHA monotherapy).

Financial implications (versus NHA monotherapy as the SoC)

* 1. The resubmission updated the financial estimates when NHA monotherapy was the SoC. Compared to the November 2023 submission and the pre-PBAC response, the overall epidemiological approach was unchanged but the estimates account for some updated parameters including, the share of NHA naïve patients (discussed in Table 17), using the trial-reported median treatment duration for both arms, and including taxane-based chemotherapy costs in the model.
  2. The main changes and impact of those changes from the November 2023 submission and pre-PBAC response are summarised in Table 19.

Table 19. Changes and impact of those changes from the November 2023 submission and pre-PBAC response

| **Component** | **November 2023 submission & PBAC comments** | **Pre-PBAC response** | **Resubmission** | **Impact** |
| --- | --- | --- | --- | --- |
| **NHA-naïve** | The PBAC considered that the estimated cost was overestimated as the proportion of mCRPC patients who were NHA naïve was significantly overestimated in the submission (52% in Year 1 decreasing to 43% from Year 3 onwards in the submission) (paragraph 7.11, olaparib PSD, November 2023). | The pre-PBAC response acknowledged that the rate of NHA uptake may be higher than previously estimated; therefore, updated the NHA uptake rates from 43% in Year 3 to 38% in Year 6. | The resubmission assumed that incident patients had progressed from m0HSPC (25%), and that all of these patients (i.e., 100%) had not accessed NHAs in earlier treatment settings. This assumption may overestimate the NHA-naïve population in m0HSPC, given the potential future availability of NHAs in earlier stages. | High |
| **Time on treatment** | 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 ToT each year. This may not be clinically plausible as continuing patients may discontinue earlier than incident patients (paragraph 6.79, olaparib PSD, November 2023). | ToT was updated for NHA monotherapy (11.8 months), and olaparib and abiraterone combination therapy (based on Weibull extrapolation in the economic model). ToT for olaparib plus abiraterone was not reported in the pre-PBAC response. Half-cycle corrected mean ToT for olaparib plus abiraterone was 37.26 months, when Weibull was selected as the extrapolation function. | ToT was updated in the resubmission to reflect median ToT reported in the PROpel trial. This reduced the ToT from 41.3 months to 31.4 months for olaparib and abiraterone and from 14.3 months to 9.9 months for NHA monotherapy.  The resubmission did not address the concern about applying similar ToTs for initiating and continuing patients. | Moderate |
| **Olaparib AEMP** | $|||| | Reduced to $|||| | Unchanged from the pre-PBAC response. | High |
| **Cost offsets** | Cost offsets for reductions in use of enzalutamide or abiraterone monotherapy in mCRPC may be overestimated due to a likely overestimate of the mean ToT (14.3 months). This was higher than the DUSC analysis in April 2022 that reported an average combined ToT for abiraterone and enzalutamide of 11.8 months on the PBS (paragraph 6.79, olaparib PSD, November 2023). | The financial estimates were updated with a ToT of 11.8 months for NHA monotherapy. | The NHA ToT was adjusted based on the PROpel trial-reported median (i.e., 9.9 months), making it more consistent with the ToT advised by the DUSC (i.e., 11.8 months). | Moderate |
| **PDT costs** | The omission of taxane-based subsequent therapy and administration costs was inappropriate (paragraph 6.79, olaparib PSD, November 2023). | Unchanged. | The resubmission included the costs of acquisition and administration of docetaxel and cabazitaxel in the model. This was appropriate. | Low |

Blue shading indicates data previously seen by the PBAC.

Source: Table 4-39, p 288 of the resubmission and compiled during the evaluation.

ABI=abiraterone, *BRCA1/2*=breast cancer gene, HSPC=hormone-sensitive prostate cancer, m0CRPC=non-metastatic castrate resistant prostate cancer, m0HSPC=non-metastatic hormone sensitive prostate cancer, mCRPC=metastatic castrate resistant prostate cancer, NHA=novel hormonal agent, OLA=olaparib, PBAC=pharmaceutical benefit advisory committee, PSD=public summary document, ToT=time on treatment.

* 1. Table 20 presents the estimated use and financial impact of olaparib plus abiraterone, when NHA monotherapy is the SoC. The financial estimates used the proposed/estimated effective AEMPs/DPMQs, consistent with the Economic analysis.

Table 20. Estimation of use and financial impact of the proposed medicine (using effective prices for olaparib and assumed effective prices for NHAs, year 0: 2024)

|  | **Year 0** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** | **Total** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Estimation of number of treated patients - Incident 1L mCRPC, *BRCA1/2* positive, NHA naïve** | | | | | | | | |
| NHA initiations in 1L mCRPC | |　1 | |　1 | |　1 | |　1 | |　2 | |　2 | - | |　3 |
| - | |　1 | |　1 | |　1 | |　2 | |　2 | |　2 | |　4 |
| NHA-naïve patients | |　1 | |　1 | |　1 | |　1 | |　1 | |　1 | - | |　5 |
| - | |　1 | |　1 | |　1 | |　1 | |　1 | |　1 | |　2 |
| *BRCA1/2*-positive patients | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 | - | |　1 |
| - | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 |
| Patients treated with OLA+ABI | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 | - | |　1 |
| - | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 |
| Reduction in 2L OLA patients | |　6 | -　|　6 | -　|　6 | -　|　6 | -　|　6 | -　|　6 | - | -　|　6 |
| - | |　6 | -　|　6 | -　|　6 | -　|　6 | -　|　6 | -　|　6 | -　|　6 |
| Patients initiating 2L chemo after progression on OLA+ABI | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 | - | |　6 |
| - | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 |
| OLA+ABI scripts dispensed | |　1 | |　2 | |　2 | |　2 | |　2 | |　5 | - | |　7 |
| - | |　1 | |　1 | |　1 | |　1 | |　1 | |　1 | |　3 |
| **Estimated financial implications of olaparib plus abiraterone** | | | | | | | | |
| Net cost of OLA+ABI to PBS/RPBS | |　8 | |　9 | |　10 | |　10 | |　10 | |　10 | - | ||11 |
| - | |　8 | |　8 | |　8 | |　9 | |　9 | |　9 | ||12 |
| **Estimation changes in financial impact of currently listed treatments** | | | | | | | | |
| Cost offsets | |　13 | |　13 | |　13 | |　13 | |　13 | |　13 | - | ||13 |
| - | |　13 | |　13 | |　13 | |　13 | |　13 | |　13 | ||13 |
| **Net financial implications** | | | | | | | | |
| Net cost to PBS/RPBS | $　|　8 | $　|　8 | $　|　9 | $||10 | $||10 | $||10 | - | $||14 |
| - | |　8 | |　8 | |　8 | |　8 | |　8 | |　8 | ||15 |
| Net cost to MBS | |　8 | |　8 | |　8 | |　8 | |　8 | |　8 | - | |　8 |
| - | |　8 | |　8 | |　8 | |　8 | |　8 | |　8 | |　8 |
| Net change to health budgeta | **|**8 | **|**8 | **|**9 | **||**10 | **||**10 | **||**10 | **-** | **||**14 |
| |　8 | |　8 | |　9 | |　9 | |　9 | |　9 | - | ||16 |
| - | **|**8 | **|**8 | **|**8 | **|**8 | **|**8 | **|**8 | **||15** |

Blue shading indicates data previously seen by the PBAC.

Source: Table 4-3, p160, Table 4-8, p163, Table 4-10, p164, Table 4-13, p166, Table 4-21, p169, Table 4-23, p172, Table 4-27, p174, Table 4-29, p175, Table 4-30, p176, Table 4-31, p176, Table 4-33, p177, Tables 4.49 and 4.50, p293, Table 4.51, p294, Table 4.53, p296, Table 4.55, p297, Tables 4.57, p298, Table 4.59, 299, Tables 4.60 and 4.61, p300, Table 4.63, p301, Table 4.64, p302 and compiled during the evaluation.

1L=first line, 2L=second line, ABI=abiraterone, BRCA=breast cancer gene, CBZ=cabazitaxel, DTX=docetaxel, ENZ=enzalutamide, m0CRPC=non-metastatic castrate resistant prostate cancer, 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

1. Three rows represent the 6-year net change to the government health budget, based on estimates from the November 2023 submission (blue, bold), the November 2023 pre-PBAC response (blue), and the resubmission (white, bold). The pre-PBAC response reflects updates in treatment duration (NHA: 359 days, OLA+ABI: 1,133 days), NHA uptake rate (NHA naïve share decreased to 41%, 39%, and 38% in years 4-6), and a reduced olaparib price (AEMP=$| |). The resubmission includes further revisions to treatment duration, NHA uptake rate, and treatment prices.

*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 30,000 to < 40,000*

*5 10,000 to < 20,000*

*6 < 500*

*7 40,000 to < 50,000*

*8 $0 to < $10 million*

*9 $10 million to < $20 million*

*10 $20 million to < $30 million*

*11 $100 million to < $200 million*

*12 $50 million to < $60 million*

*13 net cost saving*

*14 $90 million to < $100 million*

*15 $40 million to < $50 million*

*16 $80 million to < $90 million*

* 1. The resubmission estimated a net cost to the government of approximately $40 million to < $50 million ($40 million to < $50 million for PBS and $0 to < $10 million for MBS) over the first six years of listing olaparib plus abiraterone combination therapy as a first-line treatment for mCRPC, when NHA monotherapy was the SoC. This was 57% lower than the budget impact proposed in the November 2023 submission (i.e., $90 million to < $100 million) and 49% lower than the budget impact proposed in the November 2023 pre-PBAC response (i.e., $80 million to < $90 million). This was primarily attributed to lower estimates of the eligible (i.e., NHA-naïve) population, as well as a reduction in the requested price and estimated treatment duration for olaparib compared to the November 2023 submission. The estimates in the November 2023 pre-PBAC response already accounted for the change in requested price (and other minor changes to treatment duration and uptake).
  2. The revised financial estimates in the resubmission were likely to be more accurate than those in the November 2023 submission and the related pre-PBAC response. However, the introduction of additional NHAs at earlier stages of the disease—such as enzalutamide for m0HSPC, which the PBAC will also consider in its November 2024 meeting—may result in fewer NHA-naïve patients progressing to mCRPC and subsequently initiating PARPi plus NHA treatment. The estimates were also somewhat sensitive to the assumed treatment durations.

Quality Use of Medicines

* 1. The resubmission 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

* 1. The resubmission outlined the Risk Share Arrangement (RSA) for the current olaparib monotherapy restriction, effective since April 1, 2022. This included a | |% rebate beyond the financial caps and expires on March 31, 2027. The resubmission 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 21.

Table 21. Expenditure caps for olaparib in the first and second line of mCRPC therapy

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Setting** | **2025** | **2026** | **2027** | **2028** | **2029** | **2030** |
| New listing (olaparib component) ($) | | | | | | | | | | | | |
| Olaparib offset from monotherapy ($) | | | | | | | | | | | | |
| Total olaparib costs (proposed listing) ($) | | | | | | | | | | | | |
| Olaparib monotherapy (Current deed)a ($) | | | | | | | | | | | | |
| Total PARPi cost to PBS/RPBS ($) | | | | | | | | | | | | |

Source: Table 4-68, p305 of the resubmission

Note: AEMP per pack for olaparib combination (proposed, i.e., $| | or $| | per month) is equal to olaparib monotherapy

1. Assumed timing of new olaparib combination listing align with current olaparib monotherapy deed years. Assumed expenditure caps for olaparib monotherapy remain constant after the completion of the existing deed Term.
   1. The proposed RSA carries uncertainty, primarily because of the PBS listing of more NHAs in earlier disease stages (i.e., m0HSPC), which could lead to a decrease in NHA-naïve patients in the first-line mCRPC setting and an overestimate of olaparib utilisation.

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

1. PBAC Outcome
   1. The PBAC recommended 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 economic model comparing olaparib plus abiraterone to NHA monotherapy was unreliable for decision making but noted that olaparib plus abiraterone was non-inferior in terms of effectiveness and safety compared to talazoparib plus enzalutamide, and that therefore the price of olaparib in this setting should be no higher than the price of talazoparib that was considered cost-effective at the July 2024 meeting. The PBAC considered that it would be appropriate for olaparib to join same risk sharing arrangement (RSA) as talazoparib, without adjustment to the financial caps.
   2. The PBAC noted the input from individuals, health professionals and organisations which supported the resubmission. The PBAC noted that the Medical Oncology Group of Australia (MOGA) expressed its strong support for the resubmission.
   3. The PBAC considered that the proposed place in therapy, which was for the first line treatment of mCRPC patients with *BRCA1/2* pathogenic variants and aligned with that proposed for talazoparib in July 2024, was appropriate.
   4. The PBAC noted that the resubmission was primarily based on the indirect treatment comparisons (ITCs) comparing olaparib plus abiraterone (PROpel trial) with talazoparib plus enzalutamide (TALAPRO-2 trial). Further evidence was presented comparing olaparib plus abiraterone with abiraterone monotherapy (PROpel and BRCAAWAY trials).
   5. The PBAC noted that the resubmission presented three ITCs for comparable populations enrolled in PROpel and TALAPRO-2: (i) all-comers, (ii) homologous recombinant repair (HRR) pathogenic variants, and (iii) *BRCA* pathogenic variants, with NHA monotherapy as the common comparator. The PBAC recalled that it had previously considered abiraterone and enzalutamide (i.e. the NHA common comparators) to be non-inferior in terms of comparative effectiveness (paragraph 7.6, enzalutamide PSD, July 2014). The PBAC noted that none of the ITCs demonstrated a significant difference between olaparib plus abiraterone and talazoparib plus enzalutamide in terms of radiographic progression free survival (rPFS) or overall survival (OS) (see Table 5, Table 6 and Table 7). The PBAC further noted that the results of a matching adjusted indirect comparison (MAIC) presented by Castro et al, 2024 also found no statistically significant differences between olaparib plus abiraterone and talazoparib plus enzalutamide in terms of rPFS and OS in patients with HRR or *BRCA1/2* pathogenic variants (see Figure 1). Overall, the PBAC considered that olaparib plus abiraterone was likely non-inferior compared to talazoparib plus enzalutamide in terms of efficacy.
   6. In terms of safety, the PBAC noted that the ITCs presented in the resubmission were likely not reliable as there were differences in the follow up periods of the PROpel and TALAPRO-2 trials which were not controlled for and as the resubmission presented a very large number of comparisons which increased the likelihood of finding significant differences due to chance alone. The PBAC noted that olaparib and talazoparib had differing safety profiles, but the rates of discontinuation were similar for both (17.3% of PROpel patients discontinued olaparib and 18.8% of TALAPRO-2 patients discontinued talazoparib). Overall, the PBAC considered that olaparib plus abiraterone was likely non-inferior in terms of safety compared to talazoparib plus enzalutamide.
   7. Compared to abiraterone monotherapy, the PBAC considered that olaparib plus abiraterone was superior in terms of comparative and effectiveness and inferior in terms of comparative safety. The PBAC noted that the totality of the evidence presented including the all-comer and HRR subgroup data from PROpel supported the clinical claims, but that the magnitude of the clinical benefit in the *BRCA1/2* subgroup remained uncertain given the *post hoc* nature of the subgroup analyses and small sample sizes. The PBAC, noting the small sample size and unbalanced prognostic factors at baseline, considered that the clinical evidence presented from the BRCAAWAY trial was generally consistent with the *BRCA1/2* subgroup data from the PROpel trial.
   8. The PBAC noted that the resubmission presented two economics analyses, an updated cost utility analysis (CUA) comparing olaparib plus abiraterone with NHA monotherapy and a cost-minimisation approach (CMA) versus talazoparib and enzalutamide.
   9. The PBAC noted that the CUA model was based on immature OS data and did not apply convergence, which resulted in clinically implausible survival estimates (approximately 40% of olaparib plus abiraterone patients remained alive at 7.5 years and approximately 25% were alive at 10 years). Additionally, the PBAC considered that the incremental quality adjusted life year (QALY) gains of 1.79 at 7.5 years and 2.18 at 10 years were high, uncertain and favoured olaparib. Overall, the PBAC considered that model was not reliable for decision making.
   10. The PBAC noted that the CMA presented in the resubmission compared the total costs of treatment with olaparib plus abiraterone with talazoparib plus enzalutamide over 957 days of treatment. The PBAC recalled that it had previously considered that abiraterone and enzalutamide to be non-inferior (see paragraph 7.5). Thus, the PBAC considered that the CMA could be based solely on the daily doses of olaparib and talazoparib and that the equi-effective doses were:

olaparib 300 mg twice daily (i.e. 600 mg daily) = talazoparib 0.5 mg daily

* 1. In terms of the utilisation estimate, the PBAC considered that if talazoparib plus enzalutamide was PBS listed, then the assumption that | |% of patients would be treated with olaparib plus abiraterone was likely overestimated, particularly considering the safety concerns related to the use of corticosteroids with abiraterone. The PBAC considered that an uptake rate of | |% olaparib plus abiraterone and | |% talazoparib plus enzalutamide would be more reasonable.
  2. The PBAC considered that it would be appropriate for olaparib to join the same RSA as talazoparib, without adjustment to the financial caps.
  3. In terms of the restriction, the PBAC advised that the olaparib restriction should align with that accepted for talazoparib July 2024. The PBAC considered that olaparib plus abiraterone should be available for patients with an WHO ECOG performance status score of 1 or less. Further, the PBAC considered that it would be reasonable for patients who discontinued abiraterone due to toxicity or intolerance to continue to receive olaparib.
  4. The PBAC advised that only one poly ADP-ribose polymerase inhibitor (PARPi) should be PBS subsidised per lifetime for prostate cancer. Therefore, access to either olaparib or talazoparib in the first-line metastatic setting would preclude patients from receiving olaparib monotherapy as second line treatment. The PBAC noted that flow-on changes to these restrictions would be required.
  5. The PBAC advised that the terminology “BRCA gene mutation” should be updated to “BRCA gene variant”.
  6. The PBAC noted that there would likely be delays in *BRCA1/2* testing. Thus, the PBAC considered that it would be reasonable to allow treatment of olaparib plus abiraterone to be initiated after commencing treatment with a NHA in the mCRPC setting. The PBAC noted that flow on changes would be required to the abiraterone and abiraterone plus methylprednisolone restrictions in this setting as the current restrictions would not allow a patient who had commenced with enzalutamide in the metastatic setting to switch to abiraterone (in combination with olaparib) once *BRCA1/2* status was confirmed.
  7. The PBAC considered that the proposed separate initial and continuing restrictions for olaparib could be consolidated into a single-phase agnostic restriction with 5 repeats. The PBAC advised that the number of repeats for abiraterone and abiraterone plus methylprednisolone should be increased from 2 to 5 to align with olaparib. The PBAC also recommended increasing the number of repeats for enzalutamide from 2 to 5 to improve consistency among the listings.
  8. The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for olaparib:
     1. The treatment may be expected to provide a clinically relevant improvement in efficacy, over alternative therapies, but the magnitude of benefit was uncertain;
     2. The treatment is not expected to address a high and urgent unmet clinical need because there are alternative treatment options for *BRCA1/2* variant positive mCRPC;
     3. It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
  9. The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

1. Recommended listing

8.1 Add new listing as follows:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | | | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of**  **Rpts** | **Available brands** |
| OLAPARIB | | | | | | | |
| olaparib 100 mg tablet, 56 | | | NEW | 2 | 112 | 5 | Lynparza |
| olaparib 150 mg tablet, 56 | | | NEW | 2 | 112 | 5 | Lynparza |
|  | | | | | | | |
| **Restriction Summary [new1] / Treatment of Concept: [new1A]** | | | | | | | |
|  | | **Category / Program:**  GENERAL - General Schedule (Code GE) | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:** Authority Required (immediate/real-time assessment): telephone/online | | | | | |
|  |  | **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | |
|  | **Administrative Advice:** Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) abiraterone and methylprednisolone, (iii) apalutamide, (iv) darolutamide, (v) enzalutamide. | | | | | |
|  | **Administrative Advice:** Where the term 'poly ADP-ribose polymerase inhibitor' appears in this restriction, it refers to: (i) olaparib, (ii) talazoparib | | | | | |
|  | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised. | | | | | |
|  | **Administrative Advice:** No increase in the maximum number of repeats may be authorised. | | | | | |
|  | **Administrative Advice:** Special Pricing Arrangements apply. | | | | | |
|  | | **Episodicity:** [blank] | | | | | |
| **Severity:** Castration resistant metastatic | | | | | |
| **Condition:** Carcinoma of the prostate | | | | | |
|  | | **Indication:** Castration resistant metastatic carcinoma of the prostate | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene variant | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria** | | | | | |
|  | | Patient must not have received prior PBS-subsidised novel hormonal drug in any non-metastatic setting of prostate cancer prior to commencing treatment with this drug for this condition | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance score no higher than 1 prior to treatment initiation | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must be undergoing concurrent treatment with abiraterone or abiraterone plus methylprednisolone, unless an intolerance to abiraterone or abiraterone plus methylprednisolone requires either a: (i) temporary cessation, (ii) permanent discontinuation | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The treatment must not be a PBS-subsidised benefit beyond disease progression | | | | | |
|  | | **AND** | | | | | |
|  | | **Treatment criteria:** | | | | | |
|  | | Patient must only receive subsidy for one poly ADP-ribose polymerase inhibitor per lifetime for prostate cancer | | | | | |

8.2 Flow-on changes to amend the current mCRPC listings for abiraterone and abiraterone with methylprednisolone (additions are in italics and deletions are in strikethrough):

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | | | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of**  **Rpts** | **Available brands** |
| ABIRATERONE | | | | | | | |
| abiraterone 500 mg tablet, 60 | | | 11206T | 1 | 60 | ~~2~~ 5 | Zytiga |
| abiraterone 250 mg tablet, 120 | | | 2698B | 1 | 120 | ~~2~~ 5 | Zytiga |
|  | | | | | | | |
|  | | **Category / Program:**  GENERAL - General Schedule (Code GE) | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:** Authority Required (immediate/real-time assessment): telephone/online | | | | | |
|  |  | **Caution:** The bioavailability on a mg to mg basis of abiraterone combination product and abiraterone single drug product is not equivalent. When changing between abiraterone products, exercise caution in explaining correct dosing directions to the patient. | | | | | |
|  | **Administrative Advice:** Special Pricing Arrangements apply. | | | | | |
|  | **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | |
|  | **Administrative Advice:** Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) abiraterone and methylprednisolone, (iii) apalutamide, (iv) darolutamide, (v) enzalutamide. | | | | | |
| **Restriction Summary / Treatment of Concept:** | | | | | | | |
|  | | **Episodicity:** [blank] | | | | | |
| **Severity:** Castration resistant metastatic | | | | | |
| **Condition:** Carcinoma of the prostate | | | | | |
|  | | **Indication:** Castration resistant metastatic carcinoma of the prostate | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The treatment must be used in combination with a corticosteroid | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The treatment must not be used in combination with chemotherapy | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have a WHO performance status of 2 or less | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The treatment must not be a PBS benefit where disease progression occurs whilst being treated with any of: (i) a combination treatment containing the individual drugs in one pharmaceutical benefit, (ii) the individual drugs obtained as separate pharmaceutical benefits | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must only receive subsidy for one novel hormonal drug per lifetime for prostate cancer (regardless of whether a drug was subsidised under a metastatic/non-metastatic indication); or | | | | | |
|  | | Patient must only receive subsidy for a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation; *or* | | | | | |
|  | | *Patient must have been receiving PBS-subsidised treatment with enzalutamide for castration resistant metastatic prostate cancer prior to being associated with a class 4 or 5 BRCA1 or BRCA2 gene variant* | | | | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | | | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of**  **Rpts** | **Available brands** |
| ABIRATERONE WITH MEHTYLPREDNISOLONE | | | | | | | |
| abiraterone acetate 125 mg tablet [120] (&) methylprednisolone 4 mg tablet [60], 1 pack | | | 13263C | 1 | 1 | ~~2~~ 5 | Yonsa Mpred |
|  | | | | | | | |
|  | | **Category / Program:**  GENERAL - General Schedule (Code GE) | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:** Authority Required (immediate/real-time assessment): telephone/online | | | | | |
|  |  | **Caution:** The bioavailability on a mg to mg basis of abiraterone combination product and abiraterone single drug product is not equivalent. When changing between abiraterone products, exercise caution in explaining correct dosing directions to the patient. | | | | | |
|  | **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | |
|  | **Administrative Advice:** Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) abiraterone and methylprednisolone, (iii) apalutamide, (iv) darolutamide, (v) enzalutamide. | | | | | |
| **Restriction Summary / Treatment of Concept:** | | | | | | | |
|  | | **Episodicity:** [blank] | | | | | |
| **Severity:** Castration resistant metastatic | | | | | |
| **Condition:** Carcinoma of the prostate | | | | | |
|  | | **Indication:** Castration resistant metastatic carcinoma of the prostate | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The treatment must not be used in combination with chemotherapy | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have a WHO performance status of 2 or less | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The treatment must not be a PBS benefit where disease progression occurs whilst being treated with any of: (i) a combination treatment containing the individual drugs in one pharmaceutical benefit, (ii) the individual drugs obtained as separate pharmaceutical benefits | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must only receive subsidy for one novel hormonal drug per lifetime for prostate cancer (regardless of whether a drug was subsidised under a metastatic/non-metastatic indication); or | | | | | |
|  | | Patient must only receive subsidy for a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation; *or* | | | | | |
|  | | *Patient must have been receiving PBS-subsidised treatment with enzalutamide for castration resistant metastatic prostate cancer prior to being associated with a class 4 or 5 BRCA1 or BRCA2 gene variant* | | | | | |

8.3Amend talazoparib plus enzalutamide recommended restrictions as follows (additions are in italics and deletions are in strikethrough):

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | | | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of**  **Rpts** | **Available brands** |
| TALAZOPARIB | | | | | | | |
| talazoparib 0.5 mg capsule, 30 | | | TBC | 1 | 30 | 5 | Talzenna |
| talazoparib 0.35 mg capsule, 30 | | | TBC | 1 | 30 | 5 | Talzenna |
| talazoparib 0.25 mg capsule, 30 | | | TBC | 1 | 30 | 5 | Talzenna |
| talazoparib 0.1 mg capsule, 30 | | | TBC | 1 | 30 | 5 | Talzenna |
|  | | | | | | | |
| **Restriction Summary [TBC] / Treatment of Concept: [TBC]** | | | | | | | |
|  | | **Category / Program:**  GENERAL - General Schedule (Code GE) | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:** Authority Required (immediate/real-time assessment): telephone/online | | | | | |
|  |  | **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | |
|  | **Administrative Advice:** Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) abiraterone and methylprednisolone, (iii) apalutamide, (iv) darolutamide, (v) enzalutamide. | | | | | |
|  | ***Administrative Advice:*** *Where the term 'poly ADP-ribose polymerase inhibitor' appears in this restriction, it refers to: (i) olaparib, (ii) talazoparib* | | | | | |
|  | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised. | | | | | |
|  | **Administrative Advice:** No increase in the maximum number of repeats may be authorised. | | | | | |
|  | **Administrative Advice:** Special Pricing Arrangements apply. | | | | | |
|  | | **Episodicity:** [blank] | | | | | |
| **Severity:** Castration resistant metastatic | | | | | |
| **Condition:** Carcinoma of the prostate | | | | | |
|  | | **Indication:** Castration resistant metastatic carcinoma of the prostate | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene variant | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria** | | | | | |
|  | | Patient must not have received prior PBS-subsidised novel hormonal drug in any non-metastatic setting of prostate cancer prior to commencing treatment with this drug for this condition | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance score no higher than 1 prior to treatment initiation | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must be undergoing concurrent treatment with enzalutamide, unless an intolerance to enzalutamide requires either a: (i) temporary cessation, (ii) permanent discontinuation | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The treatment must not be a PBS-subsidised benefit beyond disease progression | | | | | |
|  | | **AND** | | | | | |
|  | | **Treatment criteria:** | | | | | |
|  | | *Patient must only receive subsidy for one* *poly ADP-ribose polymerase inhibitor per lifetime for prostate cancer* | | | | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | | | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of**  **Rpts** | **Available brands** |
| ENZALUTAMIDE | | | | | | | |
| enzalutamide 40 mg capsule, 112 | | | 10174L | 1 | 112 | ~~2~~ *5* | Xtandi |
|  | | | | | | | |
|  | | **Category / Program:**  GENERAL - General Schedule (Code GE) | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:** Authority Required (immediate/real-time assessment): telephone/online | | | | | |
|  |  | **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | |
|  | **Administrative Advice:** Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) abiraterone and methylprednisolone, (iii) apalutamide, (iv) darolutamide, (v) enzalutamide. | | | | | |
|  | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised | | | | | |
|  | **Administrative Advice:** No increase in the maximum number of repeats may be authorised | | | | | |
|  | **Administrative Advice:** Special Pricing Arrangements apply. | | | | | |
| **Restriction Summary / Treatment of Concept:** | | | | | | | |
|  | | **Episodicity:** [blank] | | | | | |
| **Severity:** Castration resistant metastatic | | | | | |
| **Condition:** Carcinoma of the prostate | | | | | |
|  | | **Indication:** Castration resistant metastatic carcinoma of the prostate | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The treatment must not be used in combination with chemotherapy | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have a WHO performance status of 2 or less | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must only receive subsidy for one novel hormonal drug per lifetime for prostate cancer (regardless of whether a drug was subsidised under a metastatic/non-metastatic indication); or | | | | | |
|  | | Patient must only receive subsidy for a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation; *or* | | | | | |
|  | | Patient must have been receiving PBS-subsidised treatment with abiraterone or abiraterone plus methylprednisolone for castration resistant metastatic prostate cancer prior to being associated with a class 4 or 5 BRCA1 or BRCA2 gene ~~mutation~~ *variant* | | | | | |

8.4Amend the olaparib second line listing follows (additions are in italics and deletions are in strikethrough):

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | | | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of**  **Rpts** | **Available brands** |
| OLAPARIB | | | | | | | |
| olaparib 100 mg tablet, 56 | | | 12932P | 2 | 112 | 2 | Lynparza |
| olaparib 150 mg tablet, 56 | | | 12929L | 2 | 112 | 2 | Lynparza |
|  | | | | | | | |
| **Restriction Summary / Treatment of Concept:** | | | | | | | |
|  | | **Category / Program:**  GENERAL - General Schedule (Code GE) | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:** Authority Required (immediate/real-time assessment): telephone/online | | | | | |
|  |  | **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | |
|  | **Administrative Advice:** Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) abiraterone and methylprednisolone, (iii) apalutamide, (iv) darolutamide, (v) enzalutamide. | | | | | |
|  | **Administrative Advice:** Where the term 'poly ADP-ribose polymerase inhibitor' appears in this restriction, it refers to: (i) olaparib, (ii) talazoparib | | | | | |
|  | **Administrative Advice:** Special Pricing Arrangements apply. | | | | | |
|  | | **Episodicity:** [blank] | | | | | |
| **Severity:** Castration resistant metastatic | | | | | |
| **Condition:** Carcinoma of the prostate | | | | | |
|  | | **Indication:** Castration resistant metastatic carcinoma of the prostate | | | | | |
|  | | **Treatment Phase:** Initial treatment | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene ~~mutation~~ *variant* | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria** | | | | | |
|  | | The treatment must not be subsidised in combination with: (i) chemotherapy, (ii) a novel hormonal drug | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | The condition must have progressed following prior treatment that included a novel hormonal drug for this condition (metastatic/non-metastatic disease) | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have a WHO performance status of 2 or less | | | | | |
|  | | **AND** | | | | | |
|  | | **Treatment criteria:** | | | | | |
|  | | Patient must be undergoing treatment with ~~this drug~~ *a* *poly ADP-ribose polymerase inhibitor* for the first time | | | | | |

***These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

1. 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.

1. Sponsor’s Comment

The sponsor had no comment.

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 [↑](#footnote-ref-2)
2. Hussain M, Kocherginsky M, Agarwal N et al. Abiraterone, olaparib, or abiraterone + olaparib in first-line metastatic castration-resistant prostate cancer with DNA repair defects (BRCAAWAY). *Clinical Cancer Research* 2024(c) <https://doi.org/10.1158/1078-0432.CCR-24-1402> [↑](#footnote-ref-3)
3. Castro E, Wang D, Haltner A et al. Matching-adjusted indirect comparisons (MAICs) of talazoparib plus enzalutamide (TALA+ENZA) versus olaparib plus abiraterone and prednisone/prednisolone (OLAP+AAP) for first-line (1L) therapy in patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair mutations (HRRm)/*BRCA*m. Meeting Abstract 2024 ASCO Annual Meeting. *Genitourinary Cancer – Prostate, Testicular and Penile* 2024. Poster 5063. [↑](#footnote-ref-4)
4. Svensson J., 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. [↑](#footnote-ref-5)
5. Verry, C., Pattern of Clinical Progression Until Metastatic Castration-Resistant Prostate Cancer: An Epidemiological Study from the European Prostate Cancer Registry. Target Oncol. 2022 Jul;17(4):441-451. [↑](#footnote-ref-6)