

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

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a General Schedule Authority Required (Telephone/Online) listing for patients with human epidermal growth factor receptor 2 negative (HER2-) high risk early breast cancer (eBC) with a confirmed germline Breast Cancer Gene 1 (gBRCA1) or gBRCA2 mutation who have previously been treated with neoadjuvant or adjuvant chemotherapy. The requested population was unchanged from the March 2023 submission.
- 1.2 As for the March 2023 submission, listing was requested on the basis of a cost-effectiveness analysis versus placebo (“watch and wait”). The key components of the clinical issue addressed by the resubmission are presented in Table 1.

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

Component	Description
Population	Adult patients with BRCA-mutated HER2-negative high-risk ^a early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy
Intervention	Germline BRCA mutation test Olaparib (300 mg, twice daily, orally, until progression)
Comparator	Placebo (watch and wait)
Outcomes	Invasive disease-free survival, distant recurrence-free survival, overall survival, health-related quality of life (HRQoL)
Clinical claim	Olaparib demonstrates superior efficacy and inferior yet manageable safety when compared to placebo, in patients with HER2-negative high risk early breast cancer with a confirmed BRCA1 or BRCA2 pathogenic or likely pathogenic gene variant

Source: Table 1.2, p10 of the resubmission.

BRCA = Breast Cancer gene; HER2 = human-epidermal growth factor receptor 2; HRQoL, health related quality of life; TNBC = triple negative breast cancer.

^a Where neoadjuvant chemotherapy has occurred – confirmed residual invasive cancer in the breast and/or resected lymph nodes.

In a patient with triple negative breast cancer who has received adjuvant chemotherapy, confirmed node positive disease is present or that the primary tumour is greater than 20 mm,

In a patient with hormone receptor positive HER2- disease who has received adjuvant chemotherapy, confirmed that the patient has at least 4 positive lymph nodes.

Blue shading indicates information previously seen by the PBAC.

2 Background

Registration status

- 2.1 Olaparib was TGA registered on 5 October 2023 as monotherapy for the adjuvant treatment of adult patients with BRCA-mutated (BRCAm) HER2- high-risk eBC who have previously been treated with neoadjuvant or adjuvant chemotherapy.

2.2 Olaparib is currently TGA-approved for indications in metastatic breast cancer, ovarian cancer, adenocarcinoma of the pancreas, and prostate cancer.

Previous PBAC consideration

2.3 At the March 2023 PBAC meeting, olaparib was not recommended for the adjuvant treatment of HER2- high-risk eBC with a confirmed *gBRCA1* or *gBRCA2* mutation in patients who have previously been treated with neoadjuvant or adjuvant chemotherapy. The PBAC noted that a statistically significant result for the pre-specified primary endpoint of invasive disease free survival (IDFS) was reported from the pivotal registration study, but that the overall survival (OS) data remained immature. Olaparib was inferior to placebo in terms of safety. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was highly uncertain and unacceptably high. The PBAC considered that revisions were also required to the financial estimates (para 7.1, olaparib public summary document [PSD], March 2023 PBAC meeting). While the PBAC had advised in March 2023 that the early re-entry pathway could be utilised, the resubmission stated that due to the magnitude of the changes requested by the PBAC, the sponsor elected to submit a standard re-entry resubmission to address the concerns raised by the PBAC in March 2023.

2.4 The main PBAC concerns and how they were addressed in the resubmission are summarised in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern (Olaparib, PSD, March 2023 PBAC meeting).	How the resubmission addressed it
Restriction		
Proposed restriction criteria	<p>The PBAC had several recommendations for the proposed PBS criteria (para 3.12):</p> <ul style="list-style-type: none"> • The criteria around HER2 expression should be simplified, • The patient should not be required to have completed six cycles of chemotherapy; • The criteria with respect to patients at high risk of recurrence should be simplified, • A criterion should be added requiring initiation within 12 weeks of completing other therapy, • It is not necessary to specify that HR+ patients should have ET. • In the continuing restriction, the reference to “progression” has been replaced by “recurrence”. • The restriction should prevent combination use of olaparib and pembrolizumab. 	The proposed listing was updated (see paragraph 3.3).
Clinical		

Public Summary Document - November 2023 PBAC Meeting

Component	Matter of concern (Olaparib, PSD, March 2023 PBAC meeting).	How the resubmission addressed it
Efficacy data	<p>The data for IDFS and OS were immature and the median IDFS and OS had not been met.</p> <p>The PBAC considered that a claim of superior efficacy was supported for olaparib compared with placebo, based on immature IDFS data, and noted that the OS data also remained immature. The PBAC noted that the OlympiA trial would require a significantly longer duration of follow-up for the OS data to reach maturity, especially in the HR+ group (para 7.6).</p>	<p>The data presented in the resubmission has not changed from the previous submission. IDFS and OS remain immature.</p>
Proportion of TNBC patients in the trial vs. the Australian setting	<p>The proportion of TNBC patients (82.3%) in the key OlympiA trial was higher than that estimated for the Australian setting (12%-24%). The ESC noted that the submission's estimates were drawn from Australian studies in broader patient populations that were not limited to those with gBRCA mutations, and therefore may not be applicable to the proposed PBS population (para 6.16).</p> <p>In OlympiA, the treatment effect of olaparib versus placebo was slightly higher in the TNBC subgroup than in the HR+ subgroup, in terms of IDFS, DDFS and OS. Although the difference in treatment effect was not statistically significant across subgroups, the test for interaction was not statistically powered. As TNBC patients are potentially over-represented in OlympiA in comparison to the Australian setting, this may overestimate the effectiveness of olaparib (para 6.17 and para 6.19).</p>	<p>There is no new information, and this applicability issue remained.</p>
Safety claim	<p>The PBAC noted that the olaparib arm had a higher incidence of all AEs, a higher incidence of grade 3 or higher AEs, and a higher incidence of AEs leading to dose reduction, interruption, or discontinuation, compared to the placebo arm. The PBAC also noted that MDS/AML was a concern with PARP inhibitors. The PBAC considered that olaparib had inferior safety in comparison with placebo. (para 7.7)</p>	<p>Addressed. The safety claim in the resubmission has been modified from non-inferior safety to inferior but manageable safety.</p> <p>This did not have an effect on the economic evaluation because the approach to costing AEs was unchanged. The economic evaluation included costs associated with hospitalisations due to AEs and Grade 3-4 AEs from the trial.</p>
Economic		
Data truncation time point	<p>The PBAC considered that the truncation time point in the submission's base case (42 months) resulted in the exclusion of a substantial amount of trial data and potentially resulted in the extrapolated benefits being overestimated (para 7.9).</p>	<p>Partially addressed. The truncation time point nominated in the resubmission, i.e. 48 months, included 6 months of additional data but had the same concern as the 42-month data cut-off point used in the previous submission. This was adjusted to 54 months in the pre-PBAC response.</p>

Component	Matter of concern (Olaparib, PSD, March 2023 PBAC meeting).	How the resubmission addressed it
Respecified base case	The PBAC considered that olaparib could be considered cost-effective if the changes to the economic model were made as described in the PBAC respecified base case and the ICER was approximately \$35,000/QALY, to account for the uncertainty in modelled benefit beyond the time horizon of the trial. The PBAC noted that a significant price reduction would be necessary to meet this ICER (para 7.12).	Some of the revisions suggested by the PBAC in the respecified base case were not included in the resubmission's base case. Based on previous PBAC advice and the economic issues identified during the evaluation, the commentary proposed an alternative base case.
Assumption of reduced recurrence risk	The model assumed that the recurrence rate was reduced and was equivalent across the arms beyond 5 years and, by 10 years, no recurrences were modelled. The application of a reduced recurrence at 5 years in both arms may not be justified. It is possible that the use of olaparib could delay, rather than prevent, recurrence in some patients. The model was very sensitive to the change in the time point for reduced recurrence risk in the olaparib arm (para 6.69, 6.70, 6.71, 7.11).	Not addressed. The assumption of equal reduced recurrence risk across the two treatment arms after 5 years remained unchanged in the resubmission's economic evaluation.
Results of economic evaluations by HR status	The PBAC noted that subgroup analyses of OlympiA by HR status indicated more favourable results in the TNBC subgroup compared with the HR-positive subgroup. The PBAC considered it would be informative to see the results of the economic evaluation for the HR+ and TNBC subgroups, in addition to the ITT population (para 7.13).	Not addressed. No results by HR status were provided in the resubmission.
Financial		
Utilisation estimates	The PBAC considered that the patient numbers estimated by the submission were implausibly high and did not appropriately account for differences between the TNBC and HR+ subgroups, and that the submission had overestimated the proportion of patients that would be considered at high-risk based on the proposed eligibility criteria (para 7.14). Specific advice was provided for revised estimates to use.	The estimated patient numbers were lower in the resubmission compared with the March 2023 submission. However, estimates recommended by the PBAC were not used regarding testing uptake following olaparib listing and the proportion of HR+ patients who would be high-risk.

Source: Constructed during the evaluation.

AEs = adverse events; *BRCA* = breast cancer gene; DDFS = distant disease free survival; ET = endocrine therapy; *gBRCA* = germline *BRCA*; HR+ = hormone receptor positive; ICER = incremental cost-effectiveness ratio; IDFS = invasive disease-free survival; ITT = intention to treat; MDS/AML = myelodysplastic syndrome/acute myeloid leukaemia; OS = overall survival; PARPi = poly (ADP-ribose) polymerase inhibitor; PSD = public summary document; QALY = quality-adjusted life year; TNBC = triple negative breast cancer.

2.5 As the previous submission was a streamlined codependent submission, it was also considered by MSAC at its March 2023 meeting. MSAC deferred its decision and foreshadowed that it would reconsider, if olaparib was recommended by the PBAC. MSAC considered that, in order to inform a recommendation, more information would be required on the projected patient numbers, cost of the test, and other testing requirements. The details of the MSAC consideration are documented in the ratified PSD for Application Number 1716. The sponsor submitted a streamlined MSAC resubmission alongside the PBAC resubmission, to address the matters of concern raised by the MSAC. The MBS item descriptor proposed in the resubmission is presented in Table 3. The ESC noted that the proposed population for germline *BRCA* testing is broader than the proposed population for olaparib, for example some

patients tested for germline variants at initial diagnosis may be subsequently ineligible for olaparib following surgery, or following response to chemotherapy.

Table 3: Requested MBS item descriptor

		Category 6 – Pathology Services	
MBS item NEW		Group P7 – Genetics	
Detection of germline <i>BRCA1</i> or <i>BRCA2</i> pathogenic or likely pathogenic gene variants, in a patient with triple negative early breast cancer or hormone receptor positive, HER2-negative, early breast cancer with high risk characteristics (i) tumour histological grading of at least 3, (ii) tumour size of greater than 2 cm, (iii) cancer cells in any positive axillary lymph nodes, requested by a specialist or consultant physician, to determine eligibility for treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor under the Pharmaceutical Benefits Scheme (PBS)			
Maximum one test per lifetime			
Fee: \$1,000.00	Benefit: 75% = \$750.00	85% = \$850.00*	
Explanatory note PN.0.27			
Patients who are found to have any form of affected allele should be referred for post-test genetic counselling as there may be implications for other family members. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist.			

Source: Table 1.8, p29 of the resubmission

BRCA = Breast cancer gene, *HER2* = human epidermal growth factor receptor 2.

- 2.6 The proposed schedule fee was reduced to \$1,000 in the resubmission, compared with \$1,200 in the March 2023 submission. However, a schedule fee of \$1,200 was proposed for the MBS item for *gBRCA* testing to determine the eligibility of olaparib for eBC, based on stakeholder consultation feedback. The PBAC noted that the cost of the test remains for MSAC consideration.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	DPMQ	Max. qty packs	Max. qty units	No. of Rpts	Available brands
olaparib					
Olaparib tablets, 150mg and 100mg.	Published: \$6,632.63 Effective: \$■(submission); \$■ (pre-PBAC response)	2	56	5 (initial) 7 6 (continuing)	Lynparza

Category / Program: General Schedule
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Episodicity: Adjuvant treatment of
Severity: early stage
Condition: breast cancer
Indication: Adjuvant treatment of early stage breast cancer
Treatment Phase: Initial treatment
Clinical criteria:
The condition must be negative for human epidermal growth factor receptor 2 (<i>HER2</i>) overexpression
AND

Public Summary Document - November 2023 PBAC Meeting

Clinical criteria:
Patient has completed at least six cycles (or experience toxicity necessitating withdrawal) of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or both agents.
AND
Clinical criteria:
The treatment must be adjuvant to surgical resection
AND
Clinical criteria:
The condition must be associated with a class 4 or 5 <i>BRCA1</i> or <i>BRCA2</i> gene mutation
AND
Clinical criteria:
For the first PBS authority application only, where applicable, confirm the following: <ul style="list-style-type: none"> i) Where neoadjuvant chemotherapy has occurred – confirm that residual invasive cancer is in the breast and/or resected lymph nodes. ii) In a patient with triple negative breast cancer who has received adjuvant chemotherapy, confirm that node positive disease is present or that the primary tumour is greater than 20 mm, iii) In a patient with hormone receptor positive, HER2-negative disease who has received adjuvant chemotherapy, confirm that the patient has at least 4 positive lymph nodes.
AND
Clinical criteria:
The treatment must not be a PBS-subsidised benefit beyond whichever comes first: (i) a total of 52 weeks of treatment (including any non-PBS supply), (ii) disease recurrence/progression
AND
Clinical criteria
The treatment must be commenced within 12 weeks of completing other therapy, noting this could include surgery, radiotherapy or chemotherapy
Prescribing Instructions:
Retain all pathology imaging and investigative test results in the patient’s medical records. Do not submit copies of these as part of the authority application.
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: 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: Patients may qualify for PBS-subsidised treatment under this restriction once only.

Blue shading indicates information previously seen by the PBAC.

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Episodicity: Adjuvant treatment of
Severity: early stage
Condition: breast cancer
Indication: Adjuvant treatment of early stage breast cancer
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have received previous treatment with this drug as adjuvant therapy for this condition
AND
Clinical criteria:
Patient must not have developed disease recurrence while receiving treatment with this drug for this condition
AND
Clinical criteria:
The treatment must not be a PBS-subsidised benefit beyond whichever comes first: (i) a total of 52 weeks of treatment (including any non-PBS supply), (ii) disease recurrence/progression
Prescribing Instructions:
Retain all pathology imaging and investigative test results in the patient's medical records. Do not submit copies of these as part of the authority application.
Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicessaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
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: Patients may qualify for PBS-subsidised treatment under this restriction once only.

Blue shading indicates information previously seen by the PBAC.

- 3.1 The resubmission requested listing of two strengths of olaparib tablets, 150 mg, and 100 mg. The recommended dose of olaparib is 300 mg (two 150 mg tablets) taken orally, twice daily, equivalent to a total daily dose of 600 mg. The proposed maximum quantity (112 tablets) provides sufficient tablets for 28 days of treatment at the recommended daily dose. A 100 mg tablet is also available should dose reductions be required.
- 3.2 The sponsor requested a Special Pricing Arrangement (SPA) for olaparib for the treatment of *BRC*Am, HER2-, eBC. The proposed effective dispensed price for maximum quantity (DPMQ) is \$|, based on the proposed effective ex-manufacturer price of \$|, with current fees applied. This was |% lower than the effective DPMQ proposed in the previous submission (\$|). The resubmission price (effective DPMQ of \$|; 112 tablets) approximately equals the price that PBAC considered cost-effective for olaparib in castration resistant metastatic carcinoma of the prostate in November 2021 and newly diagnosed homologous recombination deficiency (HRD) positive *BRCA* wild type advanced epithelial ovarian, fallopian tube or primary peritoneal cancer in July 2023 (effective DPMQ: \$|; 112 tablets). The pre-PBAC response proposed a further price reduction to a DPMQ of \$| (AEMP = \$|).

- 3.3 The proposed PBS restrictions have been revised in the resubmission based upon previous advice from the PBAC (para 3.12, olaparib PSD, March 2023 PBAC meeting):
- In the previous submission, patients who are HR+ were required to receive concurrent treatment with ET. This has been removed.
 - The wording for the requirement for patients to be negative for HER2 overexpression has been simplified.
 - A requirement for patients to commence treatment with olaparib within 12 weeks of completing other therapy has been added. This is consistent with the OlympiA trial.
 - The proposed PBS criteria with respect to the definition of patients at high risk of recurrence has been simplified.
 - In the continuing restriction, the reference to “progression” has been replaced by “recurrence”.
 - The PBAC recommended that the criterion “Patient has completed at least six cycles (or experience toxicity necessitating withdrawal) of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or both agents”, should be deleted. This criterion is still included in the revised proposed restriction.
 - The PBAC recommended that the restriction should prevent combination use of olaparib and pembrolizumab as this combination is unlikely to be cost-effective and there is a lack of safety and efficacy data to support it. This change has not been included in the revised proposed restriction.
- 3.4 The PBAC previously advised that if olaparib is PBS listed in eBC, it may be appropriate to clarify in the current PBS listings for poly (ADP-ribose) polymerase inhibitors (PARPis) in ovarian cancer that prior use of PARPi is in the context of the stated PBS indication, such that the restriction is not inadvertently interpreted as an intent to prevent these patients from accessing PARPi in a different cancer (para 3.8, olaparib PSD, March 2023 PBAC meeting).

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

4 Population and disease

- 4.1 Breast cancer is the most common cancer affecting Australian women. If caught in the early stages, patients can have a 5-year survival of 91%¹. However, there are several prognostic factors that can modify the chance of disease recurrence after initial treatment. Among these are the hormone receptors (HR) and human epidermal

¹ Australian Institute of Health and Welfare. Cancer in Australia 2021. 2021. Canberra, AIHW.

growth factor receptor 2 (HER2)². Cancers that do not express these disease modifiers are designated as triple negative breast cancer (TNBC). TNBC does not respond to drugs that specifically target HR and HER2 and so patients are treated with chemotherapy. Additionally, TNBC is typically more aggressive and at a high risk of recurrence³. A further prognostic factor is the presence of mutations in the *BRCA1* and *BRCA2* genes. Mutations in these genes confer an increased risk of developing several cancers including breast, ovarian, and pancreatic cancer. This increased risk also extends to disease recurrence⁴.

- 4.2 *BRCA* mutations, as well as the high-risk characteristics detailed in the proposed restriction⁵, cause increased rates of disease recurrence in TNBC and HR+ eBC patients. There remains an unmet need for therapies that can prevent or delay disease recurrence in these populations.
- 4.3 Current clinical management after initial treatment in HER2-, *BRCAm* tumours, in high-risk eBC patients, is monitoring for disease recurrence, or “watch and wait”. The patients in the key trial and in the proposed restriction can be divided into HR+ breast cancer or TNBC, that is, HR-negative (HER2-, HR-). Endocrine therapy (ET) is given in patients with HR+ cancers (i.e. not for TNBC patients), but no other specific guidelines or recommendations exist⁶. The clinical management algorithm would change by introducing testing for *gBRCA* mutations after patients are tested for hormone receptors. Patients who are positive for *BRCA* mutations would receive adjuvant olaparib after initial treatment while being monitored for recurrence. The proposed listing would allow *BRCAm* patients to be eligible for adjuvant olaparib for 1 year or until disease progression.
- 4.4 Olaparib is an orally active inhibitor of human poly (ADP-ribose) polymerase enzymes. It acts to prevent repair of single strand DNA breaks, resulting in the accumulation of mutations and eventual genetic instability. This is especially effective in cancers that

² Pourzand A, Fakhree MB, et al. Hormone receptor status in breast cancer and its relation to age and other prognostic factors. *Breast Cancer (Auckl)*. 2011;5:87-92.

³ Diana A, Carlino F, et al. Early Triple Negative Breast Cancer: Conventional Treatment and Emerging Therapeutic Landscapes. *Cancers (Basel)*. 2020;12(4).

⁴ Mehrgou, A. and M. Akouchekian (2016). "The importance of *BRCA1* and *BRCA2* genes mutations in breast cancer development." *Med J Islam Repub Iran* 30: 369.

⁵ eBC with a high risk of recurrence is defined as any of the following:

- a) Where neoadjuvant chemotherapy has occurred – confirmed residual invasive cancer in the breast and/or resected lymph nodes.
- b) In a patient with triple negative breast cancer who has received adjuvant chemotherapy, confirmed that node positive disease is present or that the primary tumour is greater than 20 mm,
- c) In a patient with hormone receptor positive, HER2-negative disease who has received adjuvant chemotherapy, confirmed that the patient has at least 4 positive lymph nodes.

⁶ Cancer Australia. Recommendations for the management of early breast cancer in women with an identified *BRCA1* or *BRCA2* gene mutation or at high risk of a gene mutation. <https://www.canceraustralia.gov.au/publications-and-resources/cancer-australia-publications/recommendations-management-early-breast-cancer-women-identified-brca1-or-brca2-gene-mutation-or-high>

already have issues with DNA repair, such as *BRC*Am cancers which lack functional components of the homologous recombination repair pathway⁷.

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

5 Comparator

- 5.1 The resubmission nominated placebo (watch and wait) as the main comparator. At the March 2023 meeting, the PBAC considered placebo (watch and wait) to be an appropriate comparator (para 7.4, olaparib PSD, March 2023 PBAC meeting). The PBAC also considered that most hormone receptor positive (HR+) patients will receive ongoing ET combined with olaparib as occurred in OlympiA; however, it was not necessary to mandate the use of ET in these patients and this may unduly disadvantage some HR+ patients that may not be appropriate for ET or experience intolerance (para 7.4, olaparib PSD, March 2023 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The PBAC also acknowledged the input received in relation to the March 2023 submission from individuals (13) and organisations (5). The comments described a desire for olaparib to be made available and noted benefits including improved survival and quality of life, and ability to return to work. The comments also noted the prohibitive cost of treatment if not subsidised and highlighted the needs of patients with triple negative breast cancer, noting that no targeted treatments are available for this patient group currently.
- 6.3 As per March 2023, the PBAC noted and welcomed input from the Medical Oncology Group of Australia (MOGA), as well as Pink Hope and the Breast Cancer Network Australia (BCNA).
- 6.4 The MOGA again expressed its strong support for the olaparib submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the OlympiA trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for olaparib of A (the highest grade in the curative setting), based on a comparison with placebo.⁸

⁷ Gouloze SC, Cohen AF, Rissmann R. Olaparib. *Br J Clin Pharmacol*. 2016;81(1):171-3.

⁸ Cheryn NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

- 6.5 Pink Hope again supported the olaparib listing, noting the high clinical need for patients with *BRCA* mutations and the impact of the disease on patients including fear of recurrence and reduced survival.
- 6.6 The BCNA supported the proposed listing on the basis of the OlympiA trial. As well as improved survival, the BCNA highlighted the psycho-social benefits from the addition of targeted treatment rather than watch and wait for this high-risk group. Along with Pink Hope, BCNA noted that without public subsidy for both the *BRCA* testing and olaparib, there would be inequitable access to treatment with the benefits only being available to those who could self-fund.

Clinical trials

- 6.7 The resubmission was based on one head-to-head trial comparing olaparib to placebo (n=1,836), the OlympiA trial.
- 6.8 Details of this trial and the associated reports are provided in Table 4. The key trial has not changed from the previous submission. Two additional citations were identified during the updated literature search carried out for the resubmission. However, the data presented in these publications – the OS results from the pre-specified second interim analysis (Geyer et al 2022) and the results for the patients from Japan in the OlympiA (Yamauchi et al 2023) – were seen by the PBAC at the March 2023 meeting.

Table 4: Trials and associated reports presented in the resubmission.

Trial ID	Protocol title/ Publication title	Publication citation
OlympiA NCT02032823	A randomised, double-blind, parallel group, placebo-controlled multicentre Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline <i>BRCA1/2</i> mutations and high-risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.	Interim Clinical Study Report; 12 July 2021
	Olaparib as Adjuvant Treatment in Patients With Germline <i>BRCA</i> Mutated High-Risk HER2 Negative Primary Breast Cancer. 2014	https://clinicaltrials.gov/ct2/show/NCT02032823
	No author listed. Adjuvant Olaparib Improves Disease-Free Survival in Early, High-Risk, <i>BRCA</i> Mutated, HER2- Breast Cancer	Oncologist 2012; 26 (suppl 3): S3-S4
	A. N. James Tutt, B. Kaufman, R. D. Gelber, et al. OlympiA: A randomised phase III trial of olaparib as adjuvant therapy in patients with high-risk HER2-negative breast cancer (BC) and a germline <i>BRCA1/2</i> mutation (g <i>BRCAM</i>).	Journal of Clinical Oncology. Conference 2015;33(15 SUPPL. 1)
	A. Tutt, J. E. Garber, B. Kaufman, et al. OlympiA: A phase III, multicentre, randomised, placebo-controlled trial of adjuvant olaparib after (Neo)adjuvant chemotherapy in patients with germline <i>BRCA1/2</i> mutations and high-risk HER2-negative early breast cancer.	Journal of Clinical Oncology. Conference: American Society of Clinical Oncology Annual Meeting, ASCO 2021;39(18 SUPPL)
	A. N. J. Tutt, J. E. Garber, B. Kaufman, et al, for the OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant Olaparib for Patients with <i>BRCA1</i> - or <i>BRCA2</i> -Mutated Breast Cancer	New England journal of medicine 2021; 384(25):2394-2405

Trial ID	Protocol title/ Publication title	Publication citation
	A. N. J. Tutt, J. Garber, R. D. Gelber, et al. VP1-2022: prespecified event driven analysis of Overall Survival (OS) in the OlympiA phase III trial of adjuvant olaparib (OL) in germline <i>BRCA1/2</i> mutation (gBRCAm) associated breast cancer.	Annals of oncology 2022;33(5):566-568
	Geyer, C., Garber, J., Gelber, R., et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in <i>BRCA1/2</i> and high-risk, early breast cancer.	Annals of Oncology 2022; 33(12):1250-1268
	Yamauchi, H., Toi, M., Takayama, S., et al. Adjuvant olaparib in the subset of patients from Japan with <i>BRCA1</i> - or <i>BRCA2</i> -mutated high-risk early breast cancer from the phase 3 OlympiA trial.	Breast Cancer 2023; 30(4):596-605

Source: Table 2.5, pp42-43 of the resubmission.

Blue shading indicates information previously seen by the PBAC.

6.9 The key features of the direct randomised trial are summarised in Table 5.

Table 5: Key features of included evidence.

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
olaparib vs. placebo						
OlympiA	1836 (1830 women and 6 men)	R, DB, PC, MC 3.5 years	Low	HER2 negative, <i>BRCA</i> mutated, eBC ⁹ previously treated with chemotherapy.	Primary outcome: IDFS. Secondary outcomes: OS, DDFS, FACIT-Fatigue, EORTC QLQ-C30, safety.	IDFS EORTC QLQ-C30

Source: Figure 2.3, p45, table 2.6, pp47-48, table 2.8 pp50-54, table 2.15, pp66-67, table 2.11, p59 of the resubmission.

BRCA = breast cancer gene, DB = double blind, DDFS = distant disease-free survival, eBC = early breast cancer, EORTC = European Organisation for the Research and Treatment of Cancer, FACIT = functional assessment of chronic illness therapy, HER2 = human epidermal growth factor receptor 2; IDFS = invasive disease-free survival, MC = multi-centre, OS = overall survival, PC = placebo controlled, QLQ-C30 = quality of life questionnaire core 30, R = randomised.

Blue shading indicates information previously seen by the PBAC.

6.10 Initially the OlympiA trial only included TNBC patients. After the trial had begun, an amendment to the protocol was made to include HR+, HER2- eBC patients. This change after study initiation explains why TNBC patients make up most of the trial population (82.3% TNBC and 17.7% HR+, HER2-) when TNBC in the Australian eBC population is estimated to be between 12-24%, although as noted by the ESC previously, this estimate may not be applicable to the proposed PBS population (para 6.10, olaparib PSD, March 2023 PBAC meeting).

6.11 The trial protocol allowed concurrent endocrine therapy (ET) for patients who were HR+. In the OlympiA trial, the olaparib arm had 168 HR+ patients with 146 (86.9%) on ET while the placebo arm had 157 HR+ patients with 145 (92.4%) on ET. In total, 325 patients were HR+ and 291 (89.5%) received concurrent ET.

⁹ Patients could be positive or negative for hormone receptors. This was a stratification factor during randomisation.

Comparative effectiveness

- 6.12 The data presented in the resubmission to support the claim of superior effectiveness was unchanged from the previous submission. The primary outcome for the OlympiA trial was IDFS. This involved investigator assessed recurrence of invasive disease or death. No minimally clinically relevant change was stated for this measure.
- 6.13 The PBAC considered that a claim of superior efficacy was supported for olaparib compared with placebo, based on immature IDFS data. The PBAC also noted that while the OS data were immature, the OlympiA trial would require a significantly longer duration of follow-up for the OS data to reach maturity (para 7.6, olaparib PSD, March 2023 PBAC meeting). The Pre-Sub-Committee Response (PSCR) stated that the duration of follow-up reported for OlympiA of 80 months was longer than clinical trials for trastuzumab emtansine (KATHERINE; maximum follow-up for OS was approximately 62 months) and abemaciclib (monarchE; maximum follow-up for OS <60 months). The ESC noted that the median follow-up for OlympiA was approximately 42 months (3.5 years), compared with 41 months in KATHERINE¹⁰ when trastuzumab emtansine was recommended by the PBAC in November 2019 (paragraph 6.22 PSD November 2019), and 42 months in monarchE¹¹ when abemaciclib was recommended by the PBAC in March 2023 (paragraph 7.7 PSD March 2023).
- 6.14 A summary of the key efficacy outcomes from the OlympiA trial is presented in Table 6.
- 6.15 There was a statistically significant reduction (37%) in the hazard of IDFS events associated with the olaparib arm compared to the placebo arm at a median follow-up of 3.5 years (14.5% in olaparib, 22.6% in placebo, hazard ratio (HR) = 0.63; 95% CI: 0.50, 0.78 at data cut-off 2 [DCO2] [12 July 2021]). The Kaplan-Meier (KM) curves for IDFS in the OlympiA trial are presented in Figure 1. The median IDFS was not reached in either treatment group at DCO2. The OlympiA trial is ongoing with an estimated completion date of May 2029.
- 6.16 Secondary outcomes included OS and distant disease-free survival (DDFS). The OS data were immature at DCO2 (75 [8.1%] deaths in olaparib and 109 [11.9%] deaths in placebo) owing to the long survival seen in eBC patients. The OS results from the OlympiA trial are displayed in Table 6. At DCO2 (median follow-up 3.5 years), there was a statistically significant reduction (32%) in the hazard of death associated with the olaparib arm compared to the placebo arm of the trial (HR = 0.68; 95% CI: 0.50,

¹⁰ Trastuzumab emtansine PSD November 2019 (for the treatment of adjuvant therapy of patients with HER2 positive eBC with residual disease following HER2-targeted neoadjuvant therapy)

¹¹ Abemaciclib PSD March 2023 (for abemaciclib in combination with standard adjuvant endocrine therapy (ET), for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), lymph node positive, invasive, resected early breast cancer (EBC) at high risk of disease recurrence)

0.91). The median OS had not been reached. The KM curves for OS in the OlympiA trial are presented in Figure 2.

6.17 DDFS results were consistent with those for IDFS. The olaparib arm had a distant recurrence rate of 11.6% while the placebo arm had a distant recurrence rate of 18.8% at DCO2. There was a statistically significant reduction in the hazard of DDFS events associated with the olaparib arm compared with the placebo arm (11.6% in olaparib vs. 18.8% in placebo, HR = 0.61; 95% CI: 0.48, 0.77).

Table 6: Results of key outcomes in the OlympiA trial DCO2 (median follow up of 3.5 years)

Outcome	Olaparib n/N (%)	Placebo n/N (%)	Hazard ratio ^b (95% CI)	Median time to event
IDFS	134 /921 (14.5%)	207/ 915 (22.6%)	0.63 (0.50, 0.78)	NR
OS	75/921 (8.1%)	109/ 915 (11.9%)	0.68 (0.50, 0.91)	NR
DDFS	107/921 (11.6%)	172/ 915 (18.8%)	0.61 (0.48, 0.77)	NR

Source: Table 2.18, p72, table 2.20, p75, and table 2.19, p73 of the resubmission.

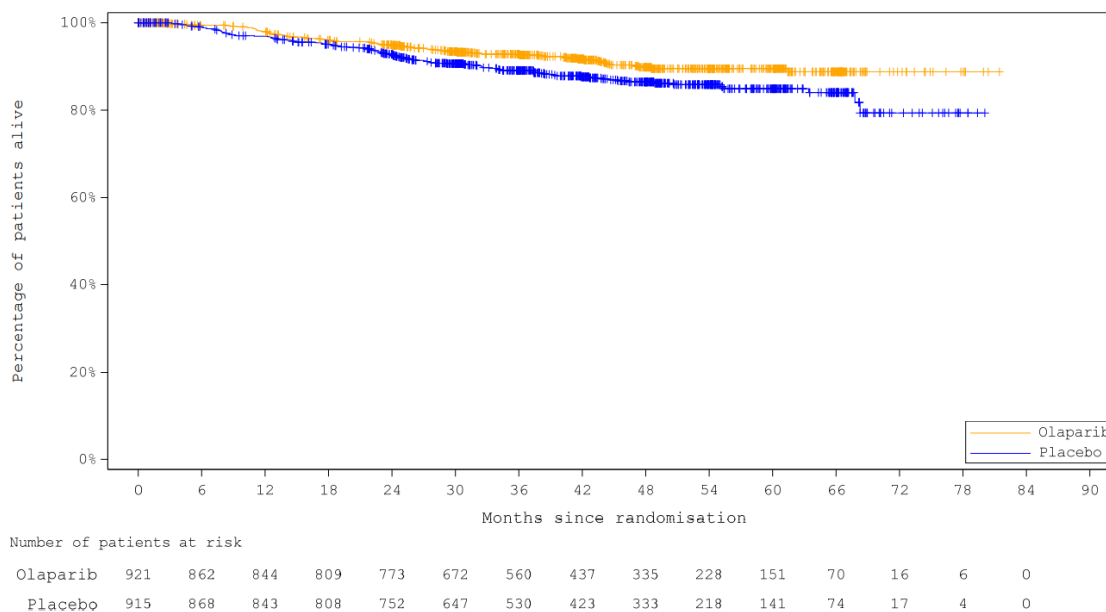
CI = confidence interval; DCO = data cut-off; DDFS = distant disease-free survival; IDFS = invasive disease-free survival; n = number of participants with event; N = total participants in group; NR = not reached; OS = overall survival.

Bold = statistically significant.

^a The resubmission noted that 95% CIs were exploratory, not inferential. For OS only, the hazard ratio with 98.5% CI was reported to be inferential according to the alpha spending rules for the DCO2 interim analysis (HR 0.68 (98.5% CI 0.47, 0.97)).

Blue shading indicates data previously seen by the PBAC.

Figure 1: Kaplan-Meier Plot for IDFS (ITT Population) in OlympiA

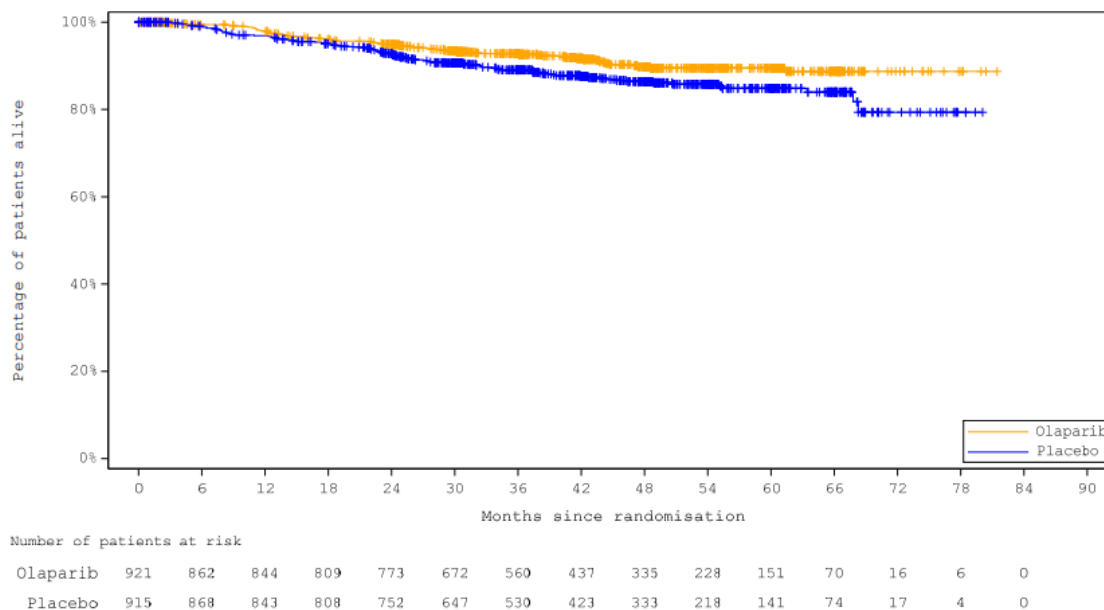


Source: Figure 2.3, p68 of the resubmission.

IDFS = Invasive disease-free survival, ITT = Intention-to-treat

Note: Median follow-up of 3.5 and 3.6 years in the olaparib and placebo arms, respectively.

Figure 2: Kaplan-Meier Plot for OS (ITT Population) in OlympiA



Source: Figure 2.5, p71 of the resubmission.

ITT = intention to treat, OS = overall survival.

Note: Median follow-up of 3.5 and 3.6 years in the olaparib and placebo arms, respectively.

Subgroup analyses

- 6.18 The presented subgroup analyses have not changed from the previous submission. Hormone receptor status was a stratification factor in the OlympiA trial, which included a smaller proportion of HR+/HER2- patients (17.7%) compared to the TNBC population (82.3%). In contrast, the resubmission estimated the proportion of HR+, HER2- patients in Australian clinical practice is between 56.9% to 79.6% compared with 12% to 24% for TNBC.
- 6.19 The hazard ratios between the HR+/HER2- population and the TNBC population are largely similar for IDFS (0.68 vs. 0.62, respectively, $p = 0.754$) and DDFS (0.69 vs. 0.59, respectively, $p\text{-value} = 0.381$), but less similar for OS (0.90 vs. 0.64, respectively, $p = 0.608$; Table 6, olaparib PSD, March 2023 PBAC meeting). There were few deaths across both treatment arms for the HR+/HER2- population ($n=16$ events in the olaparib arm vs $n=17$ events in the placebo arm). OlympiA was not statistically powered for an assessment of treatment-effect modification by TNBC vs. HR+/HER2- (para 6.19, olaparib PSD, March 2023 PBAC meeting).
- 6.20 In March 2023, the PBAC considered that the results for the TNBC subgroup (IDFS HR = 0.62; 95% CI: 0.49, 0.79) were more certain than those for the HR+ subgroup (IDFS HR = 0.68; 95% CI: 0.40, 1.13) given the larger number of TNBC patients included in the trial (82.3% of the intention to treat [ITT] population), and the longer duration of follow-up in this subgroup. Additionally, the PBAC considered that although there was no statistical evidence of treatment-effect modification on the HR-scale, it was

possible that an underlying pattern of treatment-effect modification might be revealed with more mature data (para 7.13, olaparib PSD, March 2023 PBAC meeting).

- 6.21 The type of chemotherapy that patients received (neoadjuvant or adjuvant) was also a stratification factor for randomisation. The proportion of neoadjuvant and adjuvant patients was well balanced in both the olaparib arm (50.1% adjuvant and 49.9% neoadjuvant) and placebo arm (49.7% adjuvant and 50.3% neoadjuvant). For IDFS, the hazard ratios were similar across the adjuvant and neoadjuvant subgroups (0.612 vs. 0.622, respectively, p-value = 0.763). The hazard ratios for OS (adjuvant = 0.783 vs. neoadjuvant = 0.638, p-value = 0.753) and DDFS (adjuvant = 0.562 vs. neoadjuvant = 0.623, p-value = 0.583) were slightly different across subgroups, the interaction p-values were not statistically significant (Table 7, olaparib PSD, March 2023 PBAC meeting). OlympiA was not statistically powered for these comparisons.

Patient reported outcomes

- 6.22 Patient reported outcomes were measured with FACIT-Fatigue and EORTC QLQ-C30. The compliance rate for the QoL questionnaires was similar across both arms of the study (starting at almost 100% and reducing to 70% at 24 months).
- 6.23 The FACIT-Fatigue scores were divided into patients who received neoadjuvant or adjuvant chemotherapy. Patients in the neoadjuvant group experienced an improvement in fatigue scores for the olaparib arm at 6 and 12 months but this was lost by 18 months. In contrast, the placebo arm did not see any improvement in fatigue scores. This was mirrored in the adjuvant chemotherapy group. The observed difference was statistically significant but did not meet the pre-established minimally clinically meaningful change threshold of 3 points.
- 6.24 The results from the EORTC QLQ-C30 showed mean baseline global health/QoL scores were comparable between the treatment arms. In the neoadjuvant group, there was a statistically significant improvement in global health/QoL scores from baseline to 24 months in the olaparib arm compared with placebo. In contrast, patients in the olaparib arm of the adjuvant chemotherapy group saw statistically significant baseline global health/QoL scores improvements compared with placebo at 6 and 12 months but this was not sustained at 24 months.

Comparative harms

- 6.25 The evidence presented to support the safety claim in the resubmission was based on the OlympiA trial and has not changed from the previous submission.
- 6.26 The previous submission made a claim of non-inferior safety for olaparib vs. placebo (watch and wait). The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data, and that olaparib was inferior to placebo in terms of safety (para 6.49, olaparib PSD, March 2023 PBAC meeting). Correspondingly, the resubmission made a claim of inferior, but manageable, safety for olaparib vs. placebo (watch and wait).

6.27 A summary of adverse events (AEs) in the OlympiA trial is presented in Table 7. Table 8 summarises most common Grade 3 or higher AEs in OlympiA.

Table 7: Summary of key adverse events in the OlympiA trial

Trial ID	Olaparib n with event/N (%)	Placebo n with event/N (%)	RR (95% CI) ^a
Any AE	836/911 (91.8%)	758/904 (83.8%)	1.09 (1.06, 1.13)
Any AE casually related to study treatment	736/911 (80.8%)	480/904 (53.1%)	1.52 (1.42, 1.63)
Any AE of CTCAE Grade ≥3	223/911 (24.5%)	102/904 (11.3%)	2.17 (1.75, 2.69)
Any AE with outcome=death	1/911 (0.1%)	2/904 (0.2%)	0.50 (0.05, 5.46)
Any SAE (including events with outcome=death)	79/911 (8.7%)	78/904 (8.6%)	1.01 (0.75, 1.36)
Any AE leading to discontinuation of study treatment	98/911 (10.8%)	42/904 (4.6%)	2.32 (1.63, 3.28)
Any AE leading to dose reduction	213/911 (23.4%)	33/904 (3.7%)	6.40 (4.49, 9.13)
Any AE leading to dose interruption	286/911 (31.4%)	99/904 (11.0%)	2.87 (2.33, 3.53)

Source: Table 2.25, p81 of the resubmission.

AE = adverse event, CTCAE = common terminology criteria for adverse events, CI = confidence interval, N = total participants in group, RR = relative risk, SAE = serious adverse event.

Bold = statistically significant.

^a Table 10, p20 olaparib PSD, March 2023 PBAC meeting.

Blue shading indicates data previously seen by the PBAC.

Table 8: Most common grade 3 or higher AEs in the OlympiA trial.

Trial ID	Olaparib N = 911	Placebo N = 904
Patients with AE of CTCAE Grade ≥3	223 (24.5)	102 (11.3)
Anaemia	79 (8.7%)	3 (0.3%)
Neutrophil count decrease	45 (4.9%)	7 (0.8%)
White blood cell count decrease	27 (3.0%)	3 (0.3%)
Fatigue	16 (1.8%)	6 (0.7%)

Source: Table 14.3.2.18, p323 of the OlympiA trial CSR tfls part C

AE = adverse event; CSR = clinical study report; CTCAE = common terminology criteria for adverse events

6.28 The resubmission provided additional data on potential safety concerns beyond those identified in the clinical trials. A periodic benefit-risk evaluation report (PBRER) was provided with the resubmission (16-Dec-2021 to 15-Dec-2022) encompassing approximately 46,818 patient years of exposure. During this PBRER period a safety update was made to the core data sheet. Sufficient evidence was found to suggest a causal relationship between olaparib and venous thromboembolism and pulmonary embolism. The draft Australian product information provided with the resubmission includes a revision to the section describing venous thromboembolic events.

Benefits/harms

6.29 A summary of the comparative benefits and harms for olaparib versus placebo is presented in Table 9. The benefits/harms data are unchanged from the previous submission.

Table 9: Summary of comparative benefits and harms for olaparib and placebo

Invasive disease-free survival (median duration of follow up 3.5 years for olaparib, 3.6 years for placebo)						
Event	Olaparib	Placebo	Absolute Difference	HR (95% CI)		
Progressed, n/N (%)	134/921 (14.5%)	207/915 (22.6%)	-	0.63 (0.50, 0.78) P<0.0001		
% Progression free at 12 months (95% CI)	93.4% (91.5, 94.9)	88.4% (86.1, 90.3)	5.0			
% Progression free at 24 months (95% CI)	89.7% (87.4, 91.6)	81.4% (78.7, 83.8)	8.3			
% Progression free at 36 months (95% CI)	86.1% (83.5, 88.3)	77.3% (74.3, 80.0)	8.8			
% Progression free at 48 months (95% CI)	82.7% (79.6, 85.4)	75.4% (72.2, 78.3)	7.3			
Overall survival (median duration of follow up 3.5 years for olaparib, 3.6 years for placebo)						
Deaths, n/N (%)	75/921 (8.1%)	109/915 (11.9%)	-	0.68 (0.48, 0.91) P=0.0091		
% Alive at 12 months (95% CI)	98.0% (96.9, 98.8)	96.9% (95.5, 97.9)	1.1			
% Alive at 24 months (95% CI)	95.0% (93.3, 96.2)	92.8% (90.9, 94.3)	2.2			
% Alive at 36 months (95% CI)	92.8% (90.8, 94.4)	89.1% (86.7, 91.0)	3.7			
% Alive at 48 months (95% CI)	89.8% (87.2, 91.9)	86.4% (83.6, 88.7)	3.4			
Distant disease-free survival (median duration of follow up 3.5 years for olaparib, 3.6 years for placebo)						
Progressed, n/N (%)	107/921 (11.6%)	172/915 (18.8%)	-	0.61 (0.48, 0.77) P=<0.0001		
% Progression free at 12 months (95% CI)	94.4% (92.6, 95.7)	90.3% (88.2, 92.1)	4.1			
% Progression free at 24 months (95% CI)	90.6% (88.4, 92.4)	84.0% (81.4, 86.3)	6.6			
% Progression free at 36 months (95% CI)	88.0% (85.5, 90.1)	81.0% (78.1, 83.5)	7.0			
% Progression free at 48 months (95% CI)	86.5% (83.8, 88.8)	79.1% (76.0, 81.8)	7.4			
Harms						
	Olaparib n/N	Placebo n/N	RR* (95% CI)	Event rate/100 patients		RD* (95% CI)
				Olaparib	Placebo	
OlympiA						
Any TEAE	736/911 (80.8)	480/904 (53.1)	1.52 (1.42, 1.63)	81/100	53/100	-27.7 (-31.83, -23.55)
AEs grade ≥3	223/911 (24.5)	102/904 (11.3)	2.17 (1.75, 2.69)	24/100	11/100	-13.2 (-16.67, -9.72)
Grade ≥3 Anaemia	79/911 (8.7%)	3/904 (0.3%)	26.13 (8.28, 82.46)	9/100	1/100	-8.3 (-10.21, -6.47)
Grade ≥3 Neutrophil count decrease	45/911 (4.9%)	7/904 (0.8%)	6.38 (2.89, 14.07)	5/100	1/100	-4.1 (-5.68, -2.65)
AEs leading to drug discontinuation	98/911 (10.8)	42/904 (4.6)	2.32 (1.63, 3.28)	11/100	5/100	-6.1 (-8.55, -3.68)

Source: Table 2.18, p72, table 2.19, p73, and table 2.20, p75, Table 2.25, p81 of the resubmission. Table 14.3.2.18, p323 of the OlympiA trial CSR tfls part C

AE = adverse event, CSR = clinical study report; CTCAE = common terminology criteria for adverse events, CI = confidence interval, DDFS = distant disease-free survival, IDFS = invasive disease-free survival, n = number of participants with event, N = total participants in group, OS = overall survival, RD = risk difference, RR = relative risk.

Bold = statistically significant.

* Table 12, p21 olaparib PSD, March 2023 PBAC meeting.

Blue shading indicates data previously seen by the PBAC.

- 6.30 Based on the direct evidence presented in the resubmission, for every 100 patients treated with olaparib in comparison with placebo over a median duration of follow-up of 3.5 years:
- Approximately 7 additional patients would remain invasive disease free at Year 4.
 - Approximately 3 fewer patients would die at Year 4.
 - Approximately 7 additional patients would remain free of distant recurrence at Year 4.
 - Approximately 8 additional patients would experience grade 3 or higher anaemia.
 - Approximately 4 additional patients would experience a grade 3 or higher neutrophil count decrease.
 - Approximately 1 to 2 patients may develop olaparib related myelodysplastic syndrome/acute myeloid leukaemia over the long term.

Clinical claim

- 6.31 The resubmission described olaparib as superior in terms of effectiveness compared with placebo and inferior, but manageable, in terms of safety compared to placebo.
- 6.32 The previous submission made the claim of superior effectiveness for olaparib over placebo in patients with HER2- high-risk eBC with a confirmed *gBRCA1* or *gBRCA2* mutation in patients who have previously been treated with neoadjuvant or adjuvant chemotherapy. The data presented in the resubmission have not changed since the previous submission and remain immature. The PBAC considered that a claim of superior efficacy was supported for olaparib compared with placebo, based on immature IDFS data (para 7.6, olaparib PSD, March 2023).
- 6.33 The previous submission made a claim of non-inferior safety. The PBAC disagreed with this claim and considered that olaparib had inferior safety in comparison with placebo (para 7.7, olaparib PSD, March 2023). Accordingly, the resubmission updated the safety claim to one of inferior, but manageable safety for olaparib compared with placebo. The evaluators considered this claim was supported by the presented evidence.
- 6.34 The PBAC agreed with ESC that the resubmission's claim that in comparison with placebo, olaparib was superior in terms of effectiveness and inferior, but manageable, in terms of safety was reasonable. The ESC noted that the resubmission did not provide any further clinical data for IDFS and OS endpoints and previously noted concerns regarding immature data were unchanged.

Economic analysis

- 6.35 The resubmission presented a stepped economic evaluation which remained based on the direct randomised trial OlympiA. The key components of the economic evaluation are presented in Table 10.

Table 10: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Adjuvant olaparib vs. placebo (no treatment).
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Outcomes	Disease-free years gained, life years gained, quality-adjusted life years gained
Time horizon	40 years in the model base case vs. 3.5-3.6 years in the key trial (OlympiA).
Methods used to generate results	Semi-Markov with time varying transition probabilities
Health states	Five health states: invasive disease-free survival (IDFS), non-metastatic recurrence (non-mBC), early-onset metastatic disease (early-onset mBC), late-onset metastatic disease (late-onset mBC), and death
Cycle length	Monthly
Transition probabilities	<p>The model had 7 transition probabilities. Transition probabilities were largely cycle specific and were calculated from survival curves.</p> <p>TP1 – IDFS to non-mBC (approx. 25% of all recurrences)</p> <ul style="list-style-type: none"> • Before 48 months – OlympiA IDFS survival curve (KM data) • To 60 months – parametric extrapolation of the OlympiA IDFS survival curve • To 10 years – externally sourced recurrence rate • After 10 years – no recurrences <p>TP2 – IDFS to mBC (approx. 75% of all recurrences). Before 24 months, metastatic recurrences move to the early-onset mBC health state. After 24 months, metastatic recurrences move to the late-onset mBC health state. Derivation of transition probabilities as for TP1.</p> <p>TP3 – IDFS to death. All-cause mortality data from ABS lifetables, applying a SMR of 1.61 to reflect higher mortality in patients with gBRCA mutations.</p> <p>TP4 – non-mBC to mBC. OlympiA survival curve from local recurrence to distant recurrence with fitted parametric function.</p> <p>TP5 – non-mBC to death. OlympiA survival curve from local recurrence to death with fitted parametric function, with adjustment for increased PARP use in the two treatment arms, especially in the placebo arm.</p> <p>TP6 – early-onset mBC to death. Data from OlympiA. Treatment-specific and with adjustment for increased PARP use in the two treatment arms, especially in the placebo arm.</p> <p>TP7 – late-onset mBC to death. Pooled survival curves from three treatments used in the metastatic setting. Each survival curve was first fitted with a parametric function.</p>
Extrapolation method	<p>The observed data for the IDFS survival curve were used until 48 months. A parametric function of best statistical fit was applied to the olaparib curve from 48 months to 60 months. The same function (despite not being the best fit) was applied to the placebo arm. This was TP1 and TP2.</p> <p>Extrapolation following 5 years occurred as a consequence of an assumed recurrence rate until 10 years, then no recurrences. This approach maintained the initial divergence of the IDFS curve for the lifetime of the model (except for the impact of background mortality, i.e. TP3).</p> <p>Other survival curves (TP4, TP5, TP6 and TP7) were extrapolated using parametric functions. TP4, TP5 and TP7 were common across the arms; whereas TP6 was treatment-specific.</p> <p>Overall survival was not ‘extrapolated’. It was a product of all transition probabilities applied in the model.</p> <p>Approximately 78% of the life years (undiscounted) occurred following the extent of trial data (79 months) in both arms. About 87% of the incremental life years (undiscounted) were accrued beyond 79 months</p>

Health related quality of life	<p>Utilities were applied to the IDFS, non-mBC, early-onset mBC and late-onset mBC health states.</p> <ul style="list-style-type: none"> • IDFS: 0.869 – OlympiA EORTC QLQ-C30 mapped to EQ-5D and then to utilities using a mapping algorithm (Crott and Briggs 2010¹²). A 0.6% disutility has been applied to the duration of olaparib treatment. • Non-mBC: 0.7875 – midway between IDFS and early-onset mBC (assumption) • Early-onset mBC: 0.706 – OlympiAD (mBC) EORTC QLQ-C30 from pre-progression state mapped to EQ-5D and then to utilities using a mapping algorithm. • Late-onset mBC: 0.678 – as for early-onset mBC but from the post-progression state.
Costs	Testing costs were estimated based on the increment between the assumed current testing rate of 74% for TNBC patients and 20% for HR+, HER2- patients, and the assumed uptake rate of 95%.

Source: Table 3.1, pp107-112 and Table 3.2, p113 of the resubmission.

ABS = Australian Bureau of Statistics; EORTC QLQ-C30 = European Organisation for Research and Treatment – Quality of Life Questionnaire for cancer patients; EQ-5D = EuroQoL five dimension scale questionnaire; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; KM = Kaplan-Meier; PARP = poly (adenosine diphosphate [ADP]-ribose) polymerase; SMR = standardised mortality ratio; TP = transition probability

Blue shading indicates these data sources and key inputs were unchanged from the previous submission.

6.36 The structure of the model remained the same as the March 2023 submission. Key differences between the previous submission and the resubmission are summarised in Table 11. A number of these changes were in response to previous PBAC consideration. The changes which did not adequately reflect the March 2023 PBAC and ESC advice, along with other economic issues are discussed below. The pre-PBAC response presented further adjustments to the base case.

Table 11: Key changes between the previous submission and the resubmission

	Input/assumption	Previous submission	PBAC/MSAC advice (March 2023 meeting)	Current resubmission	Comments
1	Price (effective DPMQ)	\$█	–	\$█ This was reduced to \$█ in the pre-PBAC response.	–
2	Unit cost of gBRCA test	\$1,200	The price for gBRCA testing to be investigated	\$1,000	Proposed fee of \$1,200 applied in alternative base case.
3	Truncation point for IDFS data	42 months	60 months	48 months. This was adjusted to 54 months in the pre-PBAC response.	Not in line with previous PBAC advice.
4	SMR applied to background mortality for BRCA patients	1.46	2	1.61 (non-mBC deaths in OlympiA vs. ABS lifetables)	Not in line with previous PBAC advice (SMR=2).
5	Risk of death from early-onset mBC	Equal across two arms, no adjustment for PARP use	Arm-specific	Arm-specific, with adjustment for increased PARP use in the mBC setting	The use of arm-specific data was appropriate, however the adjustment for increased PARP use was not adequately justified.

¹² Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. The European Journal of Health Economics. 2010;11(4):427-34.

Public Summary Document - November 2023 PBAC Meeting

	Input/assumption	Previous submission	PBAC/MSAC advice (March 2023 meeting)	Current resubmission	Comments
6	Testing rate in HR+, HER2- patients	74% (based on rate in TNBC)	20%	20%	In line with previous PBAC advice
7	Proportion of TNBC	12.1%	15% suggested for the financial analysis	15%	In line with previous PBAC advice
8	gBRCA prevalence in HR+, HER2- breast cancer	13.25%	5% suggested for the financial analysis	5%	In line with previous PBAC advice
9	Duration of olaparib treatment	10.267 months (based on trial TTD curve)	–	9.7 months (based on the mean treatment duration observed in OlympiA)	The TTD approach appears more accurate, as drug costs would be incurred at the beginning of each model cycle.
10	Proportion of patients receiving treatment in the mBC health state	100%	70% (based on the OlympiA trial)	80%	Trial data are preferred.
11	RDI for sacituzumab govitecan	100%	75%	94%	Not in line with previous PBAC advice. 94% is a likely overestimate.
12	Cost of echocardiography	Included	Not included	Included in the mBC health state. Excluded in the pre-PBAC base case.	Not in line with previous PBAC advice and not justified.
13	Disutility associated with olaparib treatment	No disutility applied	Apply disutility to treatment with olaparib (0.6%)	A disutility of 0.6% applied to the duration of olaparib treatment	In line with previous PBAC advice

Source: Table 3.1, pp107-112 of the resubmission.

ABS = Australian Bureau of Statistics; DMPQ = dispensed price for maximum quantity; gBRCA = germline breast cancer gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IDFS = invasive disease-free survival; mBC = metastatic breast cancer recurrence; PARP = poly (adenosine diphosphate [ADP]-ribose) polymerase; RDI = relative dose intensity; SMR = standardised mortality ratio; TNBC = triple-negative breast cancer; TTD = time to treatment discontinuation

Blue shading indicates data previously seen by the PBAC.

6.37 The resubmission nominated a time horizon of 40 years. This was unchanged from the previous submission and was not consistent with previous PBAC advice of a 30-year time horizon in the revised base case (Table 18, olaparib PSD, March 2023 PBAC meeting). The resubmission argued that a time horizon of 40 years was reasonable, based on the relatively young age of the model population (43 years) and the time horizon of previous eBC economic models considered by the PBAC, including the trastuzumab emtansine (T-DM1) model and the abemaciclib model. When the T-DM1 economic evaluation was reviewed, the PBAC considered that greater confidence in establishing cost-effectiveness would be derived by limiting the time horizon to 20 years, and noted this resulted in the ICER remaining within an acceptable range, namely less than \$15,000 per quality-adjusted life year (QALY) (para 6.36 and 7.12, trastuzumab emtansine PSD, November 2019 PBAC meeting). Regarding the

abemaciclib resubmission, the PBAC recalled it had previously advised that a 20-year time horizon would be more reasonable. However, in the context of more conservative treatment waning (from Year 4 to Year 7) and an older age at model entry¹³ (approximately 60 years), and given the aim of treatment is cure, the PBAC agreed with the ESC that a 30-year time horizon would be reasonable (para 7.13, abemaciclib PSD, March 2023 PBAC meeting). There are multiple differences between the T-DM1 or abemaciclib contexts and that of olaparib, limiting the applicability of comparisons. However, in both the case of T-DM1 and of abemaciclib, the PBAC recommended shorter time horizons than proposed in the current resubmission. Although an extended time horizon can capture all important differences in costs and outcomes between the two treatment arms, extrapolating costs and outcomes over a 40-year time horizon is also associated with uncertainty which may be reduced by applying a shorter time horizon.

- 6.38 The model functioned to direct recurrences, initially derived from the IDFS curve of the OlympiA trial, to recurrence health states. While there were some concerns regarding the costs and outcomes associated with non-metastatic breast cancer recurrence (non-mBC) and metastatic breast cancer recurrence (mBC) health states, they had minimal impacts on the model results, which were mainly driven by the modelled IDFS. The PSCR disagreed with the PBAC's March 2023 advice that the proportion of recurrences that are metastatic should be equal across both treatment arms. The ESC noted that the Evaluation's alternative base case (Table 15) applied equal proportions (metastatic vs non-metastatic) across both arms which was consistent with previous PBAC advice. The ESC considered that this was appropriate on the basis that a significant difference in rates had not been demonstrated between treatment groups and it was uncertain whether any difference would be maintained beyond the observed data.
- 6.39 IDFS data from the OlympiA trial were used up to 48 months (compared with a truncation time point of 42 months in the previous submissions). At 48 months, there were still a large number of patients remaining at risk for recurrence (n=586. More trial data could be reliably included in the economic model to account for PBAC's preference of observed rather than modelled data. Applying 'Criterion 2' of GebSKI et al (2018)¹⁴, data from the olaparib and placebo IDFS KM curves were likely to remain reliable up to 60 months (i.e. the time point previously advised by the PBAC). The increment in IDFS was larger at 48 months compared with 60 months (7.3% vs. 5.5%) and hence the use of 48 months potentially overestimated the treatment benefit associated with olaparib over placebo. Figure 3 shows that although the use of a later truncation point of 60 months affected the olaparib IDFS minimally (red dotted line

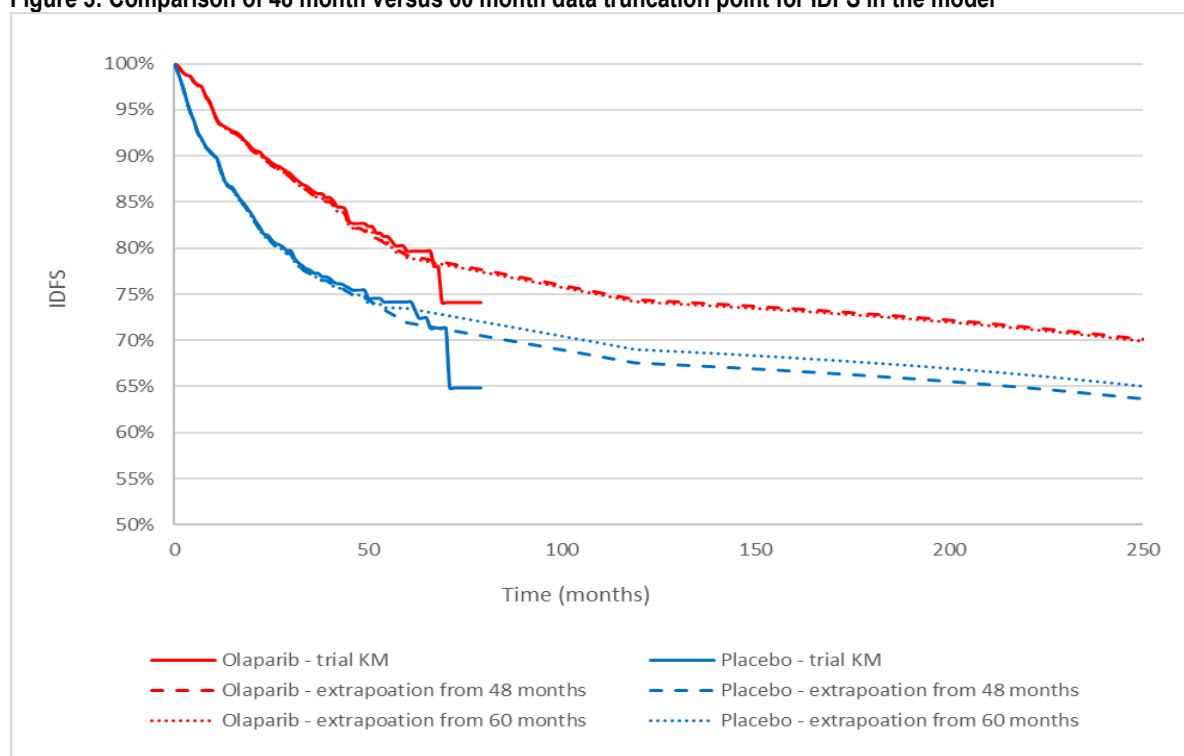
¹³ The older age of the model population would affect background mortality and result in narrower distance between the survival curves of the two treatment arms at later time points.

¹⁴ GebSKI V, Garès V, et al. Data maturity and follow-up in time-to-event analyses. *Int J Epidemiol.* 2018;47(3):850-9.

vs. red dashed line, Figure 3), it resulted in greater IDFS estimates for placebo throughout the model time horizon (blue dotted line vs. blue dashed line).

- 6.40 The PSCR stated that the truncation point should not be set beyond Month 54, based on the truncation point applied in the publication of the second interim analysis of OlympiA (Geyer 2022). The PSCR quoted email correspondence from the OlympiA trial statistician stating that “54 months was selected based on the ‘IBCSG standard rule’ – 1 year beyond the median follow-up time. As the median follow-up was 3.5 years, the curves published in Geyer 2022 were drawn to a maximum of 4.5 years (54 months). This was not pre-specified, but a very reasonable standard for publications in the medical literature.”
- 6.41 The ESC noted that data from the trial KM curves were likely to remain reliable up to 60 months based on the ‘Criterion 2’ of GebSKI et al (2018). Therefore, unless the censoring is substantially biased, the KM curves at 60 months likely represent the best estimates of IDFS for olaparib and placebo. The ESC considered that the International Breast Cancer Study Group (IBCSG) rule which nominated addition of an arbitrary period of time (1 year) does not consider the number of patients remaining at risk and that closer investigation of the data were warranted. The ESC noted that the model was sensitive to this change (Table 17). The pre-PBAC response accepted a truncation point of 54 months.

Figure 3: Comparison of 48 month versus 60 month data truncation point for IDFS in the model



Source: Generated during the evaluation, based on the “OlympiA Economic Evaluation” Excel workbook.
IDFS = invasive disease-free survival; KM = Kaplan-Meier

- 6.42 Similar to the previous submission, the resubmission assumed that the recurrence rate in patients remaining in the IDFS health state would reduce to 1% per annum (equal to 0.08% per month) from 5 years and to 0% beyond 10 years in both treatment arms. The clinical studies that informed the reduced recurrence risk were not limited to patients with high risk of recurrence and the interventions used were surgery, with or without radiation therapy and chemotherapy, thus, the recurrence-free survival observed in these studies should not inform the comparative effectiveness of adjuvant therapy with a PARP inhibitor versus placebo in the proposed high-risk population. It is unclear whether olaparib therapy results in recurrence being avoided in all patients (i.e. results in a cure), or if olaparib delays micro-metastases progressing to macro-metastases and hence delays recurrence. However, the decrease in the incremental IDFS from Year 3 to Year 5 observed in the OlympiA trial supports that olaparib delays recurrence rather than cures disease in at least a proportion of patients. A delayed time point for reduced recurrence rate in the intervention arm was considered when the National Institute for Health and Care Excellence (NICE) Appraisal Committee reviewed the economic evaluations of osimertinib and atezolizumab for early-stage non-small cell lung cancer (NSCLC) (TA761 and TA823). A sensitivity analysis was performed during the evaluation, by extending the year at which the reduced recurrence rate occurred in the olaparib arm by 1 year, i.e. from Year 5 to Year 6. The 1 year delay was selected based on the treatment duration of olaparib in the OlympiA trial (approximately 10 months).
- 6.43 To estimate transition probabilities from IDFS to death (TP3), a standardised mortality ratio (SMR) was used to capture the excess mortality risks from other illnesses in persons with *gBRCAm*. A SMR of 1.61 was calculated as the number of deaths due to non-breast cancer causes observed in OlympiA (n=11) divided by the number of deaths expected to occur over 3.5 years (i.e. the median follow-up of OlympiA) using Australian Bureau of Statistics (ABS) lifetables (n=6.8). During the relatively short observation period of OlympiA, patients had a much higher risk of disease recurrence and death as a result of *BRCAM* breast cancer than death from non-breast cancer causes. It was unlikely that the follow up in the OlympiA trial was sufficiently long enough to capture mortality from relevant *gBRCAm*-related competing risks. Therefore, the commentary considered that the SMR of 1.61 was likely underestimated. The previous PBAC respecified base case assumed a SMR of 2.0 (para 6.75, olaparib PSD, March 2023 PBAC meeting).
- 6.44 The PSCR acknowledged that the Mai 2009 SMR (1.49) used in the previous submission inappropriately excluded deaths from other cancers and noted that a literature search presented in the resubmission found a range of published estimates (1.5-2.0). The ESC noted that an SMR of 2, sourced from Levi 2002, was used in a scenario analysis suggested by the NICE evaluation group but that the final model approved by NICE incorporated an SMR of 1.49 from Mai 2009. The ESC noted that the resubmission's approach to estimation of the increase in background mortality for *gBRCAm* patients (SMR of 1.61) was based on the number of non-breast cancer deaths observed in the

OlympiA trial and considered this was reasonable and in line with published estimates. The ESC noted that changing the SMR from 2.0 to 1.61 (or vice versa) had minimal impact on the ICER. The ESC considered it was appropriate to apply an SMR of 1.61.

6.45 The transition probabilities from non-mBC to mBC (TP4), from non-mBC to death (TP5) and from early-onset mBC to death (TP6) were estimated based on the OlympiA trial data. Treatment-specific survival data, not pooled data, from the trial were used to model TP6, as per PBAC advice. The other main change was the incorporation of adjustments to nullify the impact of subsequent PARP inhibitor use for non-mBC and mBC in OlympiA, as such use of PARP inhibitor did not reflect Australian clinical practice. The adjustment factor applied to TP5 and TP6 was sourced from the OlympiAD trial which compared olaparib with chemotherapy treatment of physician's choice (TPC) in patients with gBRCAm, HER2- mBC. In the OlympiAD trial, OS benefit with olaparib was observed among patients who had not received prior chemotherapy for mBC (median OS: 22.6 months vs. 14.7 months; HR = 0.51; 95% CI: 0.29, 0.90)¹⁵. An adjustment factor of 1.961 (=1/0.51) was applied to the proportion of patients receiving PARP in mBC and non-mBC settings, with no adjustment (by applying a factor of 1) to the remaining proportion of patients who did not receive PARP. The resubmission's approach to adjustment for PARP inhibitor use was not adequately justified as:

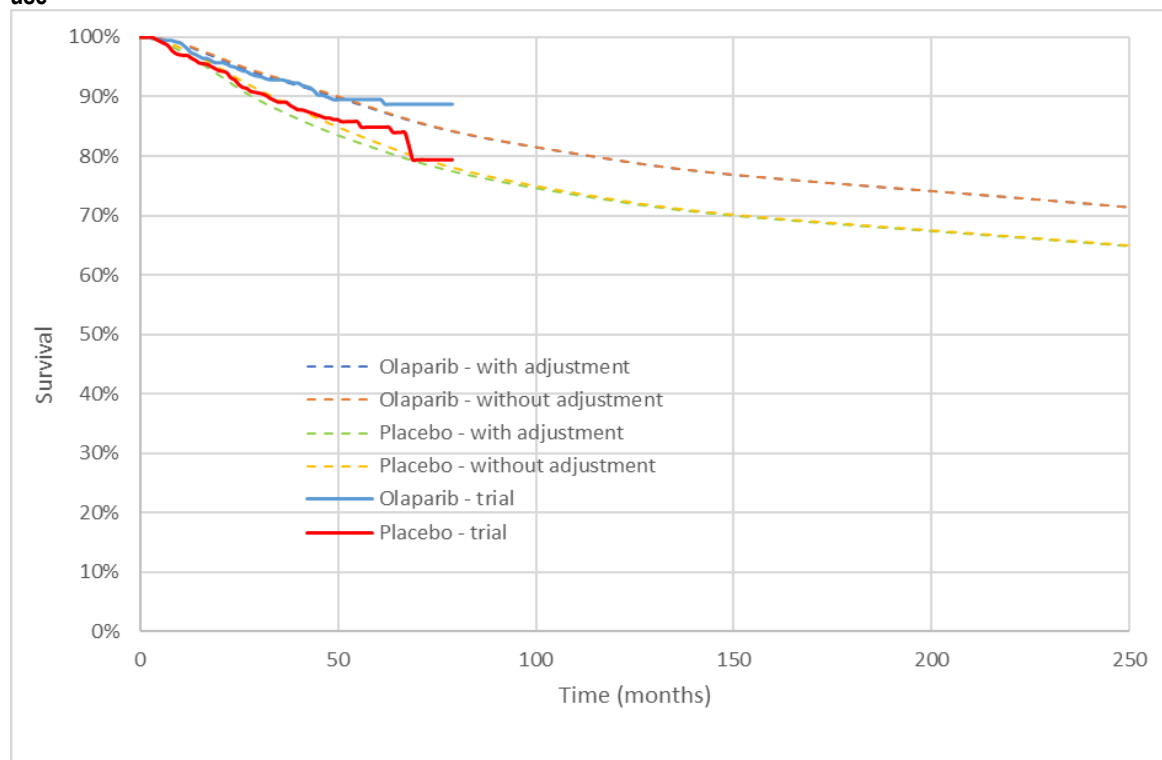
- none of the subjects in the OlympiAD trial had previously received a PARP inhibitor as adjuvant therapy. It was inappropriate to assume that the treatment effect of olaparib for mBC following adjuvant olaparib (i.e. the intervention arm of the economic model) would be the same as that reported in the OlympiAD trial.
- all patients in the OlympiAD trial had metastatic disease. It remained uncertain whether the OS benefit associated with olaparib observed in this trial can be used to inform the transition from non-mBC to death (TP5).
- the OlympiAD trial enrolled patients who had received no more than two previous chemotherapy regimens for metastatic disease. No statistically significant improvement in OS with olaparib was reported in the intention-to-treat (ITT) population (median OS: 19.3 months vs. 17.1 months; HR = 0.90; 95% CI: 0.66, 1.23). The greater benefit (HR = 0.51) was only observed among a subgroup of patients who had not previously received chemotherapy for mBC. This subgroup contained only about 29% of the ITT population. As there is no evidence indicating that, in OlympiA, patients received a PARP inhibitor as first-line therapy for metastatic recurrence only, the results from the OlympiAD ITT population, regardless of line of therapy, may be more applicable to the OlympiA trial setting and, thus, to the olaparib economic model.

¹⁵ Robson M, Tung N, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Annals of Oncology*. 2019;30(4):558-66.

Overall, there is considerable uncertainty regarding whether the PARP inhibitor use in the OlympiA trial for treatment of non-mBC and mBC could have extended the time to death as observed in the first-line treatment subgroup of the OlympiAD trial. In addition, the method of adjusting for treatment switching was not well justified and did not adhere to the methods described in the PBAC Guidelines (version 5.0). Therefore, the adjustment for TP5 and TP6 due to the use of a PARP inhibitor in the recurrence health states has been removed in the Evaluation's alternative base case analysis. The PSCR acknowledged that a simple approach was applied in the resubmission which did not adhere to the formal methods (such as RPSFT) described in the PBAC Guidelines. The ESC noted that the adjustment factor applied to the model was estimated based on the hazard ratio of OS reported in the first-line treatment subgroup of the OlympiAD trial, where no statistically significant improvement in OS with olaparib was observed in the overall mBC population. There is considerable uncertainty regarding the applicability of the subgroup results to the non-mBC setting and to the mBC setting (of all lines of therapy) of the economic model. The ESC agreed with the commentary that the method of adjustment for PARP inhibitor use was not well justified and favoured olaparib.

- 6.46 The modelled OS curves were not based on the observed OS KM curves from the OlympiA trial, but were a product of the transition probabilities in the model. A comparison of the modelled and trial-based OS shows that the modelled OS curve substantially underestimates the observed survival data for the placebo arm from early time points (green dashed line vs. red solid line, Figure 4); whereas, it provides a good fit to the observed survival data for the olaparib arm up to approximately Month 50. If the adjustment for increased PARP use in the mBC and non-mBC settings is removed, the modelled OS curve more closely matches the observed OS data for placebo (orange dashed line vs. red solid line), though still appears to underestimate the observed OS data.

Figure 4: Comparison of observed OS KM data with the modelled OS curves, with and without adjustment for PARP use



Source: Generated during the evaluation based on the economic evaluation spreadsheet.

KM = Kaplan-Meier; OS = overall survival; PARP = poly (adenosine diphosphate [ADP]-ribose) polymerase.

- 6.47 The resubmission used a *gBRCA* testing cost of \$1,000. As stated in paragraph 2.6, a Schedule fee of \$1,200 was proposed for the MBS item for *gBRCA* testing to determine the eligibility of olaparib for eBC, based on stakeholder consultation feedback.
- 6.48 The model assumed that *gBRCA* testing would be performed at or soon after diagnosis. According to the proposed MBS descriptor and proposed treatment algorithm, all TNBC patients would undergo *gBRCA* testing; whereas, of the HR+ population, about 49% patients would be considered having high-risk characteristics (i.e. tumour histology grade ≥ 3 ; tumour size ≥ 20 mm; or any positive lymph nodes) and would be eligible for *gBRCA* testing on MBS. The resubmission further assumed that 100% of patients who tested positive for *gBRCA*m at initial diagnosis would be at a high risk of recurrence and thus, eligible for adjuvant olaparib therapy, despite the broader MBS eligibility criterion for *gBRCA* testing than the PBS restriction for olaparib therapy. According to the proposed MBS and PBS listings, there will be a proportion of patients who meet the criterion for *gBRCA* testing but are subsequently ineligible for olaparib therapy following surgery¹⁶. Removing these patients from the estimation of the number of patients needed to be tested to identify one patient eligible for treatment

¹⁶ For example: i) HR+ or TNBC patients receiving neoadjuvant therapy, with no residual invasive disease; ii) TNBC patients receiving adjuvant therapy, with a primary tumour < 2 cm and without lymph node involvement; and iii) HR+ patients receiving adjuvant therapy, with < 4 positive lymph nodes.

with olaparib has underestimated the incremental costs between the two treatment arms and favoured olaparib. A sensitivity analysis was performed in which the incremental cost for testing was doubled. However, the result of this analysis should be interpreted with caution, as it did not take into account the benefits of identifying *gBRCAm* in patients who would not be eligible for olaparib, such as increased monitoring for other cancers and other preventative actions (e.g. bilateral salpingo-oophorectomy or mastectomy).

- 6.49 The PSCR acknowledged that the resubmission failed to incorporate the test cost in *gBRCA* positive patients who are ineligible for treatment (i.e., those who respond to chemotherapy) and proposed an adjustment. The PSCR assumed a chemotherapy non-response rate of 80% (equivalent to multiplying the incremental test cost by 1.25) which increased the ICER from \$35,000 to < \$45,000 /QALY in the resubmission's base case to \$45,000 to < \$55,000 /QALY. The ESC noted that 80% was the resubmission's estimate of the proportion of patients with TNBC who are at high risk for recurrence, while the proportion of high-risk patients in the HR+/HER2- population was estimated to be 39.2%(49% with high-risk characteristics × 80% with a high risk of recurrence; see Table 19). Both were higher than the March 2023 PBAC estimates (40% for TNBC and 25% for HR+/HER2-). Altering the adjustment to reflect these inputs would further increase the ICER, for example if the lowest of these proportions was used (25%), the ICER would increase to \$55,000 to < \$75,000 /QALY (with *BRCA* test cost of \$1,000 as per submission base case) or \$55,000 to < \$75,000 /QALY (with *BRCA* test cost of \$1,200).
- 6.50 The treatment duration of olaparib was sourced from the OlympiA clinical study report at DCO2, which reported a mean duration of 9.7 months in the olaparib arm after taking into account dose interruptions. The olaparib treatment duration applied to the economic model was around 0.5 months shorter than that used in the previous submission (10.27 months), which was derived from trial-based time to treatment discontinuation (TTD) curve adjusted for 12 days of treatment interruptions. The TTD approach may provide a more accurate estimate of the olaparib drug acquisition cost which would occur at the beginning of each model cycle. A sensitivity analysis was performed using a treatment duration of 10.27 months, incorporating wastage.
- 6.51 The resubmission assumed that the total proportion of patients receiving active treatment for mBC was 80%, compared with an assumption of 100% in the March 2023 submission. The PBAC previously considered 100% was an overestimate and suggested use of a treatment rate of 70%, based on the data observed in the OlympiA trial (Table 18, olaparib PSD, March 2023 PBAC meeting). The resubmission expected that the rate of treatment in the metastatic setting would increase with longer follow-up of OlympiA. The resubmission indicated that rate of mBC treatments in those who have progressed ranged from 75% to 88% based on external data sources. The resubmission assumed 80% of patients in the mBC health state undergo treatment, roughly midway between 75% and 88%. The ESC noted that while the resubmission's assumption that the mBC treatment rate might increase with extended follow-up in

the OlympiA trial might be reasonable, as the health outcomes (e.g. time from early-onset mBC to death) were modelled based on the OlympiA trial in which 70% of mBC patients received treatments, trial data on the uptake of mBC therapies would be preferable in estimating the costs for mBC treatments.

6.52 The resubmission assumed a relative dose intensity (RDI) of 94.2% for sacituzumab govitecan (SG), based on the pivotal study (ASCENT). When the SG submission was reviewed, the PBAC considered that the RDI of 94.2% was likely overestimated, given the relatively high rates of patients who experienced an AE leading to a treatment interruption (62.8% of patients in the SG arm) and dose reductions due to AEs (21.7% of patients in the SG arm). In the absence of more reliable information, the PBAC considered that a RDI of 70% to 80% may be reasonable in the context of an early resolution resubmission (para 7.15, sacituzumab govitecan PSD, November 2021 PBAC meeting). The application of a lower RDI to the mean SG dose per administration (to account for dose reductions) did not affect the treatment cost, as the number vials required per infusion would remain the same as the resubmission’s base case (4 x 180 mg vials). However, as AE-related dose interruptions occurred in more patients than dose reductions (62.8% vs. 21.7%), the evaluation’s alternative base case assumed a treatment duration of 5.6 months (compared with 6.6 months in the resubmission’s base case, a decrease of 15%) to account for dose interruptions. The model was not sensitive to this change (Table 15). The pre-PBAC response accepted a treatment duration of sacituzumab govitecan of 5.6 months.

6.53 The key drivers of the model are summarised in Table 12.

Table 12: Key drivers of the economic evaluation

Description	Method/Value	Impact Base case ICER ■■/QALY gained
Truncation point for observed data	The model used observed data up to 48 months for the IDFS curve. This was not consistent with previous PBAC advice (truncation time point of 60 months) which noted that at 60 months there were adequate data available to extend the truncation point (> 100 patients remaining at risk in each treatment arm).	High, favours olaparib. Applying a data truncation point of 60 months for the IDFS curve increased the ICER by ■■% to ■■ ³ /QALY gained.
Time horizon	The resubmission adopted a time horizon of 40 years. This was not consistent with previous PBAC advice (time horizon of 30 years).	Moderate, favours olaparib. Using a 30-year time horizon increased the ICER by ■■% to ■■ ³ /QALY gained.
Recurrence risk in the olaparib arm	The resubmission assumed the same risk of recurrence across the arms beyond 5 years, an annual recurrence rate of 1% from Year 5 to Year 10 and thereafter 0%. The validity of this assumption is difficult to test. If olaparib both avoids and delays recurrence, it may not be reasonable to assume the same time point for reduced recurrence risk between the two arms. This issue was noted previously by the PBAC.	High, favours olaparib. Delaying the application of reduced recurrence risk for olaparib by 1 year (i.e. 1% per year from Year 6 to Year 11 and 0% risk thereafter) increased the ICER by ■■% to ■■ ³ /QALY gained.
gBRCA testing cost	In estimating the number of patients needed to be tested to identify one patient who was eligible for treatment with olaparib, the resubmission assumed that 100% patients who undergo testing and test positive for gBRCA mutation at initial diagnosis would have a high risk of	Moderate to high, favours olaparib. Doubling the incremental testing cost between the two treatment arms increased the ICER by ■■% to ■■ ³ /QALY.

Description	Method/Value	Impact Base case ICER \square^1 /QALY gained
	recurrence and thus, be eligible for adjuvant olaparib therapy, despite the broader eligibility criterion for gBRCA testing than that for olaparib therapy.	

Source: Compiled during evaluation, based on Section 3.9 of the resubmission and additional sensitivity analyses performed during the evaluation.

gBRCA = germline breast cancer gene; ICER = incremental cost-effectiveness ratio; IDFS = invasive disease-free survival; QALY = quality-adjusted life years.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² < 500

³ \$45,000 to < \$55,000

- 6.54 The results of stepped economic evaluation are presented in Table 13. In the trial-based analysis (Step 1), the cost for BRCA testing was calculated as the unit cost (i.e. \$1,000), multiplied by the testing rate in the proposed scenario (95%) for the olaparib arm and by the testing rate in the HR+, HER2- patients in the current scenario (20%) for the placebo arm. The resubmission effectively assumed that, for each patient treated with adjuvant olaparib or placebo, 95% in the proposed scenario and 20% in the current scenario would need to be tested for BRCA status. This was unreasonable and has been revised during the evaluation. The cost per recurrence avoided in the trial-based analysis was also calculated during the evaluation.
- 6.55 In the resubmission, the costs and outcomes in the modelled economic evaluations (Steps 2 and 3) related to the testing population, based on the co-dependent technology model. Therefore, the costs were ‘diluted’ by the large number of non-BRCAM patients within the model. The inclusion of non-BRCAM patients had no impact on the model, as the costs and health outcomes associated with these patients would cancel out in the proposed scenario (95% testing rate + olaparib therapy if gBRCAM+) and in the comparator scenario (74% testing rate for TNBC and 20% testing rate for HR+, HER2-), apart from the BRCA testing costs. The resubmission’s economic model could be simplified to a trial (treated) population, which does not include patients without gBRCAM, but takes into account the incremental BRCA testing costs between the current and proposed scenarios per treated patient. The ICER from this simplified model was the same as that from the resubmission’s co-dependent model. For ease of interpretation and comparison with the trial-based analysis results, the costs and health outcomes presented in the modelled analyses in Table 13 relate to the treated population from the simplified co-dependent model.
- 6.56 The pre-PBAC response provided a revised base case which applied an effective DPMQ of \square (reduced from \square), assumed a truncation point of 54 months (rather than 42 months), excluded costs for echocardiograms (rather than included; consistent with the advice from the evaluation) and assumed a duration of sacituzumab govitecan treatment of 5.6 months (reduced from 6.6 months; consistent with the advice from the evaluation). The changes in the pre-PBAC response increased the base case ICER from \$35,000 to < \$45,000 per QALY in the resubmission to \$45,000 to < \$55,000 per QALY. The pre-PBAC response proposed to reduce the effective ex-manufacturer price

of olaparib from \$1 to \$1 to achieve an ICER of \$35,000 to < \$45,000 per QALY (Table 13). A summary of the changes proposed by PSCR, ESC and the pre-PBAC response is provided in Table 16.

Table 13: Results of the stepped economic evaluation

Step and component	Olaparib	Placebo	Increment
Step 1: Trial-based analysis, including BRCA test cost, olaparib drug cost and cost for treatment of AEs, over 79 months (duration of follow-up of IDFS in the OlympiA trial)			
Costs		\$1,046	
Revised ^a		\$8,328	
Invasive disease-free years gained	5.71	5.24	0.47
Recurrence-free rate (per modelled data)	77.7%	70.5%	7.2%
Incremental cost/invasive disease-free year gained			1
Revised ^a			2
Incremental cost/recurrence avoided ^{a,b}			3
Step 2: Modelled analysis (LYs)^c, as above plus costs for genetic counselling, disease monitoring, subsequent therapies, and terminal care, with time horizon extended to 40 years			
Costs		\$34,051	
LYs	14.22	13.19	1.03
Incremental cost/LY gained			4
Step 3: Modelled analysis (QALYs)^c, as above incorporating utility values			
Costs		\$34,051	
QALYs	12.27	11.36	0.91
Incremental cost/QALY gained			4
Pre-PBAC revised base case			
Costs		\$32,449	
QALYs	12.28	11.39	0.891
Incremental cost/QALY gained			4
Results of modelled economic evaluation in the March 2023 submission			
Costs		\$37,929	
QALYs	12.36	11.32	1.04
Incremental cost/QALY gained			5

Source: Table compiled during the evaluation, based on Table 3.45 to Table 3.47, p258 of the resubmission; "OlympiA Economic Evaluation" Excel workbook; and the March 2023 olaparib submission.

AEs = adverse events; BRCA = breast cancer gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IDFS = invasive disease-free survival; ICER = incremental cost-effectiveness ratio; LYs = life years; QALYs = quality-adjusted life years.

^a In estimating the BRCA testing cost in the trial-based analysis, the resubmission multiplied the unit cost (i.e. \$1,000) with the testing rate in the proposed scenario (95%) for the olaparib arm and with the testing rate in the HR+, HER2- patients in the current scenario (20%) for the placebo arm. This was inappropriate. The cost of BRCA testing to identify one treated patient in the trial-based scenario is expected to be the same as that in the modelled analysis less genetic counselling cost. This has been revised during the evaluation.

^b Additional analysis performed during the evaluation.

^c Modelled costs and outcomes are for the 'trial population' and do not include patients without BRCA mutations. This has been done so that the costs relate to a full course of olaparib per patient vs. a full course of placebo per patient. The cost per patient in the testing population relates to only 7.1% of the cost of olaparib. The ICER remains the same as the benefits are also only 7.1% of the whole population. However, the numbers are not intuitive.

Blue shading indicates results previously seen by the PBAC.

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$95,000 to < \$115,000

³ \$555,000 to < \$655,000

⁴ \$35,000 to < \$45,000

⁵ \$45,000 to < \$55,000

6.57 The disaggregated summary of health outcomes (Table 14) suggests that the life years (LYs) were predominantly accrued in the IDFS health state, with a reduction in incremental benefits related to early onset mBC and non-mBC. The LYs gained in the late onset mBC population were essentially the same between the two treatment arms. The majority (87%) of the LYs gained (undiscounted) with olaparib were accrued in the extrapolated period (79 months). The undiscounted LYs gained were accrued reasonably linearly over time. This contrasted with the incremental costs over time, which were the largest at the start of the model due to the front-loaded drug acquisition cost and cost of *BRCA* testing. The difference in cumulative costs between olaparib and placebo decreased slightly over time as a result of a higher proportion of patients receiving subsequent treatments for recurrent disease in the placebo arm.

Table 14: Disaggregated summary of health outcomes (in terms of LYs) included in the economic evaluation of the trial population

Outcome	Olaparib	Placebo	Increment	% of total increment
Discounted				
IDFS	13.56	12.38	1.19	115.4%
Non-mBC	0.37	0.42	-0.05	-5.3%
Early-onset mBC	0.08	0.19	-0.10	-10.0%
Late-onset mBC	0.20	0.20	0.00	-0.1%
Total LYs	14.22	13.19	1.03	100.0%

Source: Table generated during the evaluation, based on the "OlympiA Economic Evaluation" Excel workbook.

6.58 Based on previous PBAC advice and the concerns raised during the evaluation, the Commentary proposed an alternative base case which is presented in Table 15. The ICER from the alternative base case was estimated to be \$55,000 to < \$75,000 /QALY gained, 57% higher than the resubmission's base case. Of note, when the original olaparib submission was reviewed, the PBAC considered that olaparib could be considered cost-effective if the changes to the economic model were made as described in the PBAC respecified base case and the ICER was approximately \$35,000/QALY (para 7.12, olaparib PSD, March 2023 PBAC meeting).

Table 15: Stepwise multivariate sensitivity analyses to generate the Evaluation’s alternative base case

	Description of change	Base case value	Alternative value	ICER (cumulative)	Change in ICER
	Base case		–	█ ¹	█%
1	Observed data truncation point	48 months	60 months	█ ²	█%
2	Proportion of recurrences that are non-metastatic vs. metastatic	Treatment-specific: Olaparib: 25.0% vs. 75.0% Placebo: 23.2% vs. 76.8%	Equal across arms: 23.9 vs. 76.1% in both arms	█ ²	█%
3	Increase background mortality for gBRCA mutated patients to account for other cancer deaths	1.61	2	█ ²	█%
4	Proportion of patients with mBC who receive active treatments	80%	70%	█ ²	█%
5	Adjustment for increased PARP use for non-mBC and mBC	Included	Removed	█ ²	█%
6	Treatment duration of sacituzumab govitecan	6.6 months	5.6 months, taking to account dose interruptions	█ ²	█%
7	BRCA testing unit cost	\$1,000	\$1,200	█ ²	█%
8	Echocardiography	Included in the mBC health state	Removed	█ ²	█%
9	Model time horizon	40 years	30 years	█ ²	█%

Source: Analyses performed during the evaluation.

gBRCA = germline breast cancer gene; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; mBC = metastatic breast cancer recurrence; non-mBC = non-metastatic breast cancer recurrence; PARP = poly (adenosine diphosphate [ADP]-ribose) polymerase; TNBC = triple negative breast cancer.

^a Additional changes include: 1) duration of olaparib therapy = 10.27 months (as used in the previous economic evaluation, based on the time to treatment discontinuation curve); 2) treatment duration for sacituzumab govitecan = 5 months (≈25% reduction from the resubmission’s estimate); 3) % of TNBC = 12.1% (as assumed in the previous submission); 4) prevalence of gBRCA mutations in HR+ patients = 13.25% (as assumed in the previous submission); and 5) weighted testing rate in the current scenario of 33.5% (as respecified in the PBAC base case).

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$55,000 to < \$75,000

6.59 As noted in Table 15, the commentary proposed nine changes to the resubmission’s base case based on previous PBAC advice and the concerns raised during the evaluation. The PSCR disagreed with six of the revisions in the commentary’s alternative base case as outlined in Table 16.

Table 16: Changes proposed by PSCR, ESC and the pre-PBAC response

	Topic	PSCR	ESC Advice
1	Observed data truncation point	The PSCR proposed that the truncation point should be no later than 54 months.	The ESC agreed with the commentary that 60 months is appropriate; however, 54 months could be considered in a sensitivity analysis. 54 months was applied in the pre-PBAC response revised base case
2	Time horizon	The PSCR maintained that a time horizon of 40 years was appropriate.	The ESC agreed with the commentary that 30 years is appropriate, consistent with previous PBAC advice. The pre-PBAC response again applied a time horizon of 40 years
3	Proportion of recurrences that are metastatic (vs non-metastatic)	The PSCR maintained that treatment-specific inputs were appropriate for the proportion of recurrences that are non-metastatic vs metastatic.	The ESC noted that the Evaluation's alternative base case was consistent with previous PBAC advice and was appropriate on the basis that a significant difference in rates had not been demonstrated between treatment groups and as it was uncertain whether any difference would be maintained beyond the observed data. Unchanged in the pre-PBAC response revised base case.
4	Background mortality	The PSCR maintained that SMR of 1.61 was appropriate.	The ESC agreed with the PSCR that a value of 1.61 was appropriate.
5	Treatment of mBC	The PSCR maintained it was appropriate to assume that 80% of patients are treated for metastatic recurrence.	The ESC, noting that this change would have a minimal impact on the analysis, advised that a value of 70% was appropriate as described in the commentary. The pre-PBAC response assumed 80% of patients were treated for metastatic recurrence.
6	Adjustments for subsequent PARP inhibitor use in TP5 and TP6	The PSCR maintained that the resubmission's adjustments for TPs from non-metastatic health state to death and from metastatic health state to death due were justified for increased PARP inhibitor use.	The ESC agreed with the commentary that the method of adjustment for PARP inhibitor use was not well justified and favoured olaparib. The method was unchanged in the pre-PBAC response revised base case

mBC = metastatic breast cancer; PARP = poly (ADP-ribose) polymerase; SMR = standardised mortality ratio; TP = transition probability

6.60 Additional sensitivity analyses based on the evaluation's alternative base case and analyses proposed by the ESC are presented in Table 17.

Table 17: Sensitivity analyses presented in the commentary and additional analyses proposed by the ESC

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change to ICER
Evaluation's alternative base case		0.61	1	-
Time horizon (base case: 30 years)				
40 years		0.67	1	- %
Discount rate (base case: 5%)				
0%		1.18	1	- %
3.5%		0.73	1	- %
Assumption of reduced recurrence rate in the olaparib arm (base case: Years 5-10: 1% per year; Year 10+: 0%)				
Delayed by 1 year, i.e. Years 6-11: 1% per year; Year 11+: 0%)		0.47	2	%
gBRCA testing cost (base case: unit cost of \$1,200. Testing rate of 95% in the proposed scenario. To estimate the number needed to be tested to identify one patient treated with olaparib, it was assumed that 100% patients who undergo gBRCA testing and are tested positive for gBRCA mutation would receive olaparib therapy)				
Unit cost of \$1,000		0.61	1	- %
Testing rate of 74% for both TNBC and HR+/HER2- in the proposed scenario (the testing rate for TNBC in the current scenario)		0.6149	1	- %
Testing rate of 90% for both TNBC and HR+/HER2- in the proposed scenario (testing rate in Year 6 of listing as estimated in the financial analysis)		0.6149	1	- %
Assuming 50% of patients tested positive for gBRCA would be eligible for olaparib ^a		0.61	2	%
Treatment duration of olaparib (base case: 9.7 months)				
10.27 months (based on trial TTD)		0.61	1	%
Additional analyses proposed by the ESC				
Additional multivariate analysis: Evaluation alternative base case + truncation time point of 54 months ^b		0.74	1	- %
Additional multivariate analysis: Evaluation alternative base case + truncation time point of 54 months ^a + SMR of 1.61 ^c		0.75	1	- %
Additional multivariate analysis: Evaluation alternative base case + truncation time point of 54 months ^a + SMR of 1.61 ^c + Treatment-specific proportion of recurrences that are metastatic		0.77	1	- %
Additional multivariate analysis: Evaluation alternative base case + truncation time point of 54 months ^a + SMR of 1.61 ^c + Treatment-specific proportion of recurrences that are metastatic + BRCA test cost \$1,000		0.77	3	- %

Source: Analyses performed during the evaluation.

gBRCA = germline breast cancer gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; TNBC = triple negative breast cancer; TTD = time to treatment discontinuation.

^a This effectively doubles the incremental cost for BRCA testing between the two arms.

^b Compared with 48 months in the resubmission's base case and 60 months in the Evaluation alternative base case.

^c The same as the resubmission's base case. A SMR of 2 was assumed in the Evaluation alternative base case.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$45,000 to < \$55,000

Drug cost/patient/course

Table 18: Drug cost per patient for olaparib^a based on the effective price proposed in the resubmission

	Trial dose and duration	Model	Financial estimates
Mean dose	565 mg	600 mg ^b	600 mg ^c
Mean duration	9.7 months ^d	9.7 months ^d	9.7 months ^d
Cost/patient/month ^e (\$)			
Cost/patient/course (\$)			

Source: Table 14.3.1.1 and Table 14.3.1.4, Attachment 2.4 to the resubmission; and 'Cost of olaparib' spreadsheet, "OlympiA Economic Evaluation" and 'Att_4.1_OlympiA UCM_AZ Resubmission_FINAL.xlsx' workbooks included with the resubmission.

^a The comparator nominated in the resubmission was placebo. Therefore, the comparator costs are not included in the table above. This table does not reflect the reduced price proposed in the pre-PBAC response.

^b The mean daily dose of olaparib in the economic model was assumed to be 600 mg (full prescribed dose). This is achieved using 4 x 150 mg tablets. The relative dose intensity of 91.8% is not relevant as the reduction in dose is managed with 100 mg tablets, which are priced the same as 150mg tablets.

^c Approximately, given that 0.9% of patients were assumed to receive 100 mg scripts and 99.1% assumed to receive 150 mg scripts. The justification for the distribution of strength use was not appropriate (based on the distribution of patient category – RPBS: PBS). Depending on the dose modification, patients could receive either 400 mg (one 100 mg script per 28 days) or 500 mg per day (one of each 100 mg and 150 mg scripts per 56 days). The distribution of dosing was not reported, however due to the small proportion of 100 mg use assumed, the weighted daily dose is likely to be close to 600 mg.

^d Treatment duration after removing dose interruptions

^e Based on the resubmission's effective dispensed price for maximum quantity. The lower mean daily dose as reported in the trial due to dose interruptions did not affect the drug cost given the proposed flat pricing.

Estimated PBS usage & financial implications

6.61 The resubmission was not considered by DUSC.

6.62 The epidemiological approach presented was, in general, consistent with the previous submission, with updates to the estimates used based on advice provided by the PBAC. This approach applied epidemiological estimates to AIHW projections of breast cancer incidence to estimate the number of patients that have a high-risk of recurrence, and so would be eligible for proposed olaparib treatment. As epidemiological estimates varied across TNBC and HR+ HER2- breast cancer, eligible patients were estimated separately across cancer type.

6.63 The key inputs in the financial analysis are summarised in Table 19.

Table 19: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident cases of breast cancer	Increasing from 21,729 in Year 1 to 24,173 by Year 6 based on AIHW breast cancer incidence projections for all persons, 2022-2031 ^a	The source was unchanged from the previous submission, though incidence estimates have been updated to reflect 2024-29
Proportion of patients at Stage I-III at diagnosis	95.1% based on AIHW breast cancer incidence by stage data, 2011, adjusted for patients with unknown disease stage ^b	This change was consistent with PBAC advice (para 7.14, olaparib PSD March 2023 PBAC meeting)
Proportion of patients with TNBC	15.0% based on Cancer Council Australia, accepted by the PBAC previously (Table 16, atezolizumab PSD, March 2021 PBAC meeting)	This change was consistent with PBAC advice (para 7.14, olaparib PSD March 2023 PBAC meeting)
Proportion of TNBC that is high risk	Assumed to be 80.0%, as previous PBAC advice (40%) (para 7.14, olaparib PSD March 2023 PBAC meeting) was considered to be an underestimate, due to unknown BRCA status in the study cited, and a higher risk of recurrence could be expected in gBRCA patients (due to poor prognosis)	This may not be reasonable given that previous studies ^c suggest that response with neoadjuvant chemotherapy may be higher in those with gBRCA variants. The economic model assumed all TNBC patients tested would meet the criteria for

Public Summary Document - November 2023 PBAC Meeting

Parameter	Value applied and source	Comment
		olaparib treatment. The PBAC maintained that 40% was a more reasonable estimate.
Proportion with HR+ HER2- breast cancer	69.3% (Stuart-Harris et al. 2019) ^d	This was unchanged and was reasonable.
Proportion of HR+ HER2- breast cancer that is high risk	39.2%, assuming 49.0% of patients have high-risk characteristics eligible for testing (based on the proportion that use (neo)adjuvant therapy reported in Patiniott et.al. 2019 ^e), and that of these, 80% do not respond to treatment (as assumed for TNBC)	The PBAC reiterated that 25% would be more appropriate (para 7.14, olaparib PSD March 2023 PBAC meeting) The economic model assumed all HR+ HER2- breast cancer patients eligible for testing (i.e. 49%) would meet the criteria for olaparib treatment (paragraph 6.48).
Uptake of gBRCA testing before olaparib listing		
• TNBC	74.0%, based on PBAC advice (para 7.14, olaparib PSD March 2023 PBAC meeting)	This was reasonable.
• HR+ HER2-	20.0%, based on PBAC advice (para 7.14, olaparib PSD March 2023 PBAC meeting)	This was reasonable.
Uptake of gBRCA testing after olaparib listing		
• TNBC	74.0% in Year 1 to 90.0% from Year 3. Year 1-2 estimates were as advised by the PBAC (para 7.14, olaparib PSD March 2023 PBAC meeting). In Year 3+, a higher rate (90%) was applied as PBAC advice (85%) was considered an underestimate by the resubmission.	The basis for the claimed underestimate in Year 3+ was not clear. The applied estimates were noted to be lower than used in the economic model (95%)
• HR+ HER2-	Assumed to increase from 50.0% in Year 1 to 90.0% from Year 4 as estimates (20% in Year 1, and 30% from Year 2) advised by the PBAC (para 7.14, olaparib PSD March 2023 PBAC meeting) were considered an underestimate based on high testing uptake in advanced ovarian and prostate cancer following olaparib listing.	It is unclear whether use of testing for treatment in the advanced setting would be indicative of use of testing for treatment in the early (adjuvant) setting. The applied estimates were noted to be lower than used in the economic model (95%)
Proportion with gBRCA variants		
• TNBC	13.25% based average of Armstrong et al. (2019) ^f , Wong-Brown et al. (2015) ^g and IPSOS data (Att. 4.2 to the resubmission)	This was consistent with PBAC advice (para 7.14, olaparib PSD March 2023 PBAC meeting)
• HR+ HER2-	5.0% based on PBAC advice (para 7.14, olaparib PSD March 2023 PBAC meeting)	This was reasonable and consistent with other published literature. ^h
Uptake rate	Assumed to increase from ■■■ - ■■■%	This was unchanged and was reasonable.
Scripts dispensed	10.54 per patients based on an average of 9.7 months treatment from OlympiA	This was reasonable.
Olaparib strength	150 mg: 99.1% 100 mg: 0.9%, based on patient category PBS statistics for second-line olaparib PBS items	The use of patient category statistics (i.e. RPBS/PBS) was not appropriate and underestimates use of the 100 mg strength.
Grandfathered patients	■■■ ¹ (assumption)	The basis for this number of grandfathered patients remains unclear.
Cost of gBRCA testing	\$1,000 as per the proposed MBS item.	A schedule fee of \$1,200 was supported based on stakeholder consultation feedback. The cost of the test remains for MSAC consideration.

Source: Constructed during the evaluation from Table 4.3, pp267-8 of the resubmission.

gBRCA = germline breast cancer gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple negative breast cancer.

Blue shading indicates estimates previously seen by the PBAC.

^a Australian Institute of Health Welfare. Cancer in Australia 2021. Canberra: AIHW 2021. Cancer series no. 133. Cat. no. CAN 144.

^b Australian Institute of Health Welfare. Cancer in Australia 2019. Canberra: AIHW 2019. Cancer series no. 119. Cat. no. CAN 123.

^c Desai NV, Zakalik D, Somerfield MR, Tung NM. Q and A: A New Standard of Care for Germline *BRCA1* and/or *BRCA2* Mutation Carriers With Early-Stage Breast Cancer. *JCO Oncol Pract*. 2022 Jun;18(6):427-9.

^d Stuart-Harris R, Dahlstrom JE, Gupta R, Zhang Y, Craft P, Shadbolt B. Recurrence in early breast cancer: Analysis of data from 3,765 Australian women treated between 1997 and 2015. *The Breast*. 2019 2019/04/01;44:153-9.

^e Patiniott PD, Wong GYM, Lam YH, Fosh B. Neoadjuvant chemotherapy rates for breast cancer in Australia—"are we there yet?". *Annals of Breast Surgery*. 2019;3.

^f Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of *BRCA* mutation in breast cancer. *Clin Epidemiol*. 2019;11:543-61.

^g Wong-Brown MW, Meldrum CJ, Carpenter JE, Clarke CL, Narod SA, Jakubowska A, et al. Prevalence of *BRCA1* and *BRCA2* germline mutations in patients with triple-negative breast cancer. *Breast cancer research and treatment*. 2015;150(1):71-80.

^h Tung N, Lin NU, Kidd J, Allen BA, Singh N, Wenstrup RJ, et al. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer. *J Clin Oncol*. 2016;34(13):1460-8.

The redacted values correspond to the following ranges:

¹ < 500 patients

6.64 The resubmission’s estimates of the number of patients treated with olaparib over the first six years of listing are presented in Table 21.

Table 20: Estimated number of patients in the resubmission and amendments recommended by the PBAC

		2024	2025	2026	2027	2028	2029
	Resubmission estimates						
A	Breast cancer incidence	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
B	Patients at stage I-III at diagnosis (95.1%)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
	TNBC						
C	Patients diagnosed with TNBC (15.0% of incident breast cancer cases)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
D	Patients on (neo)adjuvant chemotherapy (100%)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
E	Uptake of <i>gBRCA</i> testing in TNBC patients (%)	█	█	█	█	█	█
F	TNBC patients tested	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
G	TNBC patients with <i>gBRCA</i> variants (13.3%)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
H	High-risk TNBC patients (80%) (estimated from proportion of TNBC patients who did not have complete response to (neo)adjuvant chemotherapy)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
I	Uptake of olaparib	█ ³ %	█ ³ %	█ ³ %	█ ³ %	█ ³ %	█ ³ %
J	TNBC patients treated with olaparib	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
	HR+ HER2- breast cancer						
K	Patients with HR+ HER2- breast cancer (69.3% of incident breast cancer cases)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
L	Patients on (neo)adjuvant chemotherapy (49.0%) used for estimation of patients eligible for testing	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
M	Uptake of <i>gBRCA</i> testing in HR+ HER2- patients (%)	█	█	█	█	█	█
N	HR+ HER2- patients tested	█ ²	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵

Public Summary Document - November 2023 PBAC Meeting

		2024	2025	2026	2027	2028	2029
O	HR+ HER2- patients with gBRCA variants (5.0%)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
P	High-risk HR+ HER2- patients (80%; estimated proportion of HR+ HER2- patients that tested positive for gBRCA variants who meet the proposed PBS eligibility requirements)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Q	Uptake of olaparib (%)	■	■	■	■	■	■
R	HR+ HER2- patients treated with olaparib	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
	Grandfathered						
S	Grandfathered patients	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
T	Total patients treated with olaparib	■ ³	■ ³	■ ²	■ ²	■ ²	■ ²
Amendments recommended by the PBAC							
Revised H	High-risk TNBC patients eligible for treatment (40% rather than 80%, see para 6.69)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Impact on J	TNBC patients treated with olaparib	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Revised L ^a	High-risk HR+ HER2- patients (25%) used for estimation of patients eligible for testing	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Impact on R	HR+ HER2- patients treated with olaparib	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Total after revisions	Total patients treated with olaparib	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³

a. Proportion applied in Row L was revised, and Row P was removed.

Source: Constructed during the evaluation from Table 4.13, p275; Table 4.15, p280; Table 4.17, pp281-2; and Table 4.19, pp282-3 of the resubmission.

gBRCA = germline breast cancer gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple negative breast cancer.

The redacted values correspond to the following ranges:

¹ 20,000 to < 30,000

² 500 to < 5,000

³ < 500

⁴ 10,000 to < 20,000

⁵ 5,000 to < 10,000

6.65 The resubmission indicated that < 500 patients would be expected to be grandfathered once olaparib was listed on the PBS. While this was reduced from the previous submission (< 500), the basis for this number of patients remains unclear. Furthermore, grandfathered patients were also assumed to receive the entire treatment course, which was not reasonable, given that they initiate treatment prior to PBS listing.

6.66 The estimated use and cost of gBRCA testing and olaparib treatment estimated in the resubmission is presented in Table 21. This table reflects the resubmission's estimates and does not reflect the amendments recommended by the PBAC (see Table 20), and does not reflect the price proposed in the pre-PBAC response.

Table 21: Base case use and financial implications estimated in the resubmission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Incremental incident patients tested	1	1	1	2	2	2
Number of cascade tests Revised ^a	1 3	1 3	1 1	1 1	1 1	1 1
Number of patients treated	3	3	1	1	1	1
Number of scripts dispensed ^b	1	1	2	2	2	2
Estimated financial implications of olaparib						
Cost to PBS/RPBS less co-payments	4	4	5	5	5	5
Net financial implications						
Net cost to PBS/RPBS	4	4	5	5	5	5
Net cost to MBS ^c	6	6	6	6	6	6
Revised ^d	6	6	6	6	6	6
Net cost to Government	4	5	5	5	5	5
Revised	4	5	5	5	5	6
Previous submission (March 2023 PBAC meeting)						
Number of patients treated	1	1	1	1	1	1
Net cost to PBS/RPBS Revised ^e	7	5	6	6	6	6
	7	8	9	10	10	10

Source: Constructed during the evaluation from Section 4 of the resubmission and from the 'Att_4.1_OlympiA UCM_AZ Resubmission_FINAL.xlsx' file.

^a Revised to reflect the incremental number of relatives tested due to the listing of olaparib.

^b Assuming 10.54 scripts per patient as estimated by the resubmission (9.7 months × (365.25 ÷ 12) = 295 days ÷ 28 day duration per script = 10.54 scripts).

^c Assuming a cost to the MBS of \$850.00 per additional patient tested. Cascade testing was not included in the base case financial estimates.

^d Revised to assume a schedule fee of \$1,200 per test in incident patients, with 85% rebate applied that accounted for the greatest permissible gap; to include the cost of incremental cascade testing only due to the listing of olaparib; and to assume a schedule fee of \$400 per relative tested (based on MBS item 73297)

^e The estimates in the previous submission were revised to correct an error that effectively only applied half the number of scripts.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ <500

⁴ \$10 million to < \$20 million

⁵ \$20 million to < \$30 million

⁶ \$0 to < \$10 million

⁷ \$30 million to < \$40 million

⁸ \$60 million to < \$70 million

⁹ \$50 million to < \$60 million

¹⁰ \$70 million to < \$80 million

6.67 The total cost to the PBS/RPBS of listing olaparib was estimated to be \$20 million to < \$30 million in Year 6, and total of \$100 million to < \$200 million over the first 6 years of listing. This was reduced from previously revised estimates of \$70 million to < \$80 million in Year 6 and \$300 million to < \$400 million over the first 6 years of listing. The reduction in cost to the PBS/RPBS was predominantly due to a reduction in the number of patients who commence treatment, though the analysis also reflects a reduction in the number of scripts per patient (from the maximum to the average number of scripts per patient, which was consistent with PBAC advice) (para 7.14, olaparib PSD, March 2023 PBAC meeting) and a reduction in the proposed effective price of olaparib.

- 6.68 In general, the March 2023 PBAC advice regarding the estimates was incorporated into the resubmission except for the extent of *gBRCA* testing uptake and proportion of patients considered to have a high-risk of recurrence. . The PBAC considered that the resubmission’s estimates of the extent of *gBRCA* testing uptake were uncertain but acceptable.
- 6.69 Eligibility for olaparib is restricted to patients who are considered to have a high risk of recurrence. The PBAC previously considered that approximately 40% of TNBC patients would meet these additional criteria, based on trial data in the neoadjuvant setting that indicated a complete response rate of 50–65% (Table 20, olaparib PSD March 2023 PBAC meeting). The resubmission applied an estimate of 80%, as it considered that *BRCA* status in this trial was unknown and that due to poorer prognoses in patients with *gBRCA* variants, a higher risk of recurrence was likely. This argument may not be reasonable given that previous studies¹⁷ suggest that the complete response rate with neoadjuvant chemotherapy may be higher in those with *gBRCA* variants. The PBAC maintained that 40% of TNBC patients would be classified as high risk, and this was based not only on an estimate of complete response rates, but also related to disease stage. For a patient to be considered high risk they would need to have Stage II/Stage III disease and not have a complete response to chemotherapy (Stage I patients not included).
- 6.70 The resubmission maintained that 49.0% of HR+ HER2– patients would have high-risk characteristics eligible for testing (i.e. tumour histology grade ≥ 3 ; tumour size ≥ 20 mm; or any positive lymph nodes). The PBAC previously considered that 25.0% would be a more appropriate estimate of the proportion at high-risk in the HR+ population. Overall, the proportion of high-risk patients estimated in the resubmission for the HR+ population was 39.2% (49% with high-risk characteristics \times 80% with a high risk of recurrence). The PBAC maintained that 25% of HR+ patients would be deemed high risk. Updated estimates are presented in Table 20 reflecting this advice.
- 6.71 The net impact to Australian Government health budgets estimated in the resubmission is presented in Table 21. These have also been revised to apply a schedule fee of \$1,200 per test in incident patients (with 85% rebate that appropriately accounted for the greatest permissible gap (GPG) allowed for MBS fees); to include the cost of incremental cascade testing only due to the listing of olaparib; and to assume a schedule fee of \$400 per relative tested (based on MBS item 73297). As mentioned in paragraph 2.6, the PSCR proposed that the MBS fee should be \$1,000. The amendments recommended by the PBAC (see Table 20) are not reflected in Table 21. The PBAC noted that the costs to the MBS remain for MSAC consideration.

¹⁷ Desai NV, Zakalik D, et al. A New Standard of Care for Germline *BRCA1* and/or *BRCA2* Mutation Carriers With Early-Stage Breast Cancer. *JCO Oncol Pract*. 2022 Jun;18(6):427-9.

Quality Use of Medicines

- 6.72 The resubmission stated that the biomarker testing ensures the provision of the most appropriate treatment for the patient, which is in line with the objectives of quality use of medicines (QUM). The sponsor-initiated activities (current and future) to promote and support QUM include educational and training programs to prescribers and patients.

Financial Management – Risk Sharing Arrangements

- 6.73 No Risk Sharing Arrangement was proposed in the resubmission, however the sponsor did indicate a willingness to work with the PBAC and Department to determine appropriate terms for PBS listing.

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

7 PBAC Outcome

- 7.1 The PBAC recommended olaparib for the treatment of patients with human epidermal growth factor receptor 2 negative (HER2-) high risk early breast cancer (eBC) with a confirmed germline Breast Cancer Gene 1 (*gBRCA1*) or *gBRCA2* mutation who have previously been treated with neoadjuvant or adjuvant chemotherapy. The PBAC noted there was a high need for effective treatment in this population, which is a small subset of breast cancer patients. The PBAC considered that the revised economic evaluation addressed most of the outstanding issues; however, an additional price reduction was required to account for remaining uncertainty in the modelled benefit of olaparib. The PBAC noted the revised financial estimates and advised that further amendments were necessary to reflect the likely use in practice.
- 7.2 The PBAC noted that the previous submission was a streamlined codependent submission and was deferred by the MSAC at its March 2023 meeting. The MSAC foreshadowed that it would reconsider if olaparib was recommended by the PBAC. The PBAC noted that an application for germline *BRCA* mutation test to detect *BRCA1* or *BRCA2* mutations in patients with HER2-negative high risk early breast cancer to determine eligibility for PBS-listed olaparib treatment (Application number 1716) will be considered by MSAC at the meeting on 23-24 November 2024.
- 7.3 The PBAC noted the input from individuals and organisations which supported the resubmission and acknowledged that the Medical Oncology Group of Australia (MOGA) had again expressed its strong support for the resubmission.
- 7.4 The PBAC noted that no additional clinical data were presented, and that the previously considered results from the OlympiA trial were presented again to support the clinical claims.
- 7.5 The PBAC recalled that in March 2023 it had considered that olaparib was superior compared with placebo in terms of efficacy although the invasive disease-free survival (IDFS) and overall survival (OS) data were immature.

- 7.6 The PBAC noted that the resubmission had updated the safety claim from ‘non-inferior’ compared to placebo to ‘inferior yet manageable’ safety when compared to placebo. The PBAC considered that this was reasonable as olaparib had a higher incidence of all adverse events.
- 7.7 The PBAC recalled that in March 2023 it had considered that olaparib could be considered cost-effective if changes were made to the economic model in conjunction with a significant price reduction. The PBAC had considered that an incremental cost effectiveness ratio (ICER) of approximately \$35,000 per quality adjusted life year (QALY) would be required to account for the uncertainty in modelled benefit beyond the trial horizon of the trial (see paragraph 7.8).
- 7.8 The PBAC noted that the resubmission presented a revised economic evaluation (see Table 11) and proposed further revisions in the pre-Sub-Committee and pre-PBAC responses, informed by advice in the evaluation and ESC advice, respectively (see Table 16). The PBAC considered the model settings described in the pre-PBAC response had adequately addressed the concern regarding extrapolation point by changing from 48 months to 54 months.
- 7.9 The PBAC considered that the primary issue outstanding was the time horizon. The PBAC considered that a 30-year time horizon would reduce the uncertainties associated with the immature trial data and align with previous PBAC decisions. The PBAC noted that the proposed population of patients with a confirmed *gBRCA1* or *gBRCA2* gene mutation was on average younger than other early BC cohorts, however considered the use of a 40 year time horizon introduced uncertainty and was inconsistent with previously accepted adjuvant BC models (Abemaciclib PSD, March 2023 PBAC meeting, paragraph 7.13; Pembrolizumab PSD, July 2023, paragraph 5.4). The PBAC therefore considered a further price reduction was required to account for the extended time horizon proposed in the pre-PBAC response, noting that a time horizon more consistent with the previously accepted 30 years would be appropriate. The PBAC noted that a further price reduction would be required to achieve an ICER of \$35,000 to < \$45,000 per QALY. The PBAC noted that it had previously required lower ICERs in this setting but considered that an ICER of \$35,000 to < \$45,000 per QALY would be acceptable in the context of the proposed listing of olaparib for patients with *BRCA* mutations, because this refers to a small subset of breast cancer patients with a high clinical need.
- 7.10 In terms of the utilisation and financial impact estimates, the PBAC considered that the patient numbers estimated by the resubmission overestimated the proportions of patients considered to have a high risk of recurrence (see Table 20). For patients with TNBC, the PBAC considered that the proportion of patients meeting PBS criteria for high risk characteristics would be 40% (see paragraph 6.69). For HR+ HER2- patients, the PBAC considered that the proportion of patients meeting PBS criteria for high risk characteristics would be 25% as advised in March 2023, noting that the financial model incorporated this estimate in two steps (see paragraph 6.70).

- 7.11 The PBAC advised that a Risk Sharing Arrangement (RSA) with [REDACTED] % rebate should be implemented with expenditure caps based on the revisions outlined in paragraph 7.10, given uncertainty with patient numbers and testing/treatment uptake.
- 7.12 The PBAC considered that the proposed restriction should include a criterion that prevented use of olaparib in combination with abemaciclib or pembrolizumab, if PBS listed for use in early breast cancer in the future.
- 7.13 The PBAC previously advised that if olaparib is PBS listed in eBC, it may be appropriate to clarify the current PBS listings for PARP inhibitors in ovarian cancer that prior use of PARP inhibitors is in the context of early breast cancer should be inadvertently interpreted as an intent to prevent these patients from accessing PARP inhibitors in a different cancer (see paragraph 3.4). The PBS listings for olaparib and niraparib in ovarian cancer include the following phrase: “Patient must not have previously received PBS-subsidised treatment with this drug for this condition”. The use of “This condition” in the text is taken to differentiate the cancer and adequately covers allowing subsequent use of these PARP inhibitors in later line for the different cancer type.
- 7.14 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:
- Olaparib is expected to provide a substantial and clinically relevant improvement in efficacy over placebo;
 - Olaparib is not expected to address a high and urgent unmet clinical need as there are alternative therapies available;
 - 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.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new listings as follows:

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OLAPARIB					
olaparib 150 mg tablet, 56	New 1	2	112	5	Lynparza

Public Summary Document - November 2023 PBAC Meeting

olaparib 100 mg tablet, 56	New 2	2	112	5	Lynparza
Restriction Summary [New 1] / Treatment of Concept [New 1A] : Authority Required					
Category / Program: GENERAL – General Schedule (Code GE)					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Indication: Adjuvant treatment of early stage breast cancer					
Treatment Phase: Initial treatment					
Clinical criteria:					
The condition must be human epidermal growth factor receptor 2 (HER2) negative					
AND					
Clinical criteria:					
<i>The patient must have received neoadjuvant or adjuvant chemotherapy. Patient has must have completed at least six cycles (or experienced toxicity necessitating withdrawal) of either (i) neoadjuvant, (ii) or adjuvant chemotherapy containing anthracyclines, taxanes, or both agents.</i>					
AND					
Clinical criteria:					
The treatment must be adjuvant to surgical resection					
AND					
Clinical criteria:					
The condition must be associated with a class 4 or 5 <i>BRCA1</i> or <i>BRCA2</i> gene mutation					
AND					
Clinical criteria:					
The patient has received: (i) neoadjuvant chemotherapy, and residual invasive cancer is confirmed in the breast and/or resected lymph nodes (pathological complete response was not achieved), or (ii) adjuvant chemotherapy for triple negative breast cancer, and has either: (a) node positive disease is present, or (b) a primary tumour greater than 20 mm, or (iii) adjuvant chemotherapy for hormone receptor positive breast cancer, and has at least 4 positive lymph nodes					
AND					
Clinical criteria:					
The treatment must not be a PBS-subsidised benefit beyond <i>the following</i> , whichever comes first: (i) a total of 52 weeks of treatment (including any non-PBS subsidised supply), (ii) disease recurrence. <i>Mark any remaining repeat prescriptions with the words 'cancelled'; where (i)/(ii) has occurred</i>					
AND					
Clinical criteria:					
The treatment must be commenced within 12 weeks of completing other therapy; noting this could include surgery, radiotherapy or chemotherapy noting that other therapy can be any of the following therapy: (i) surgery, (ii) radiotherapy, (iii) chemotherapy.					
AND					
Clinical criteria:					
<i>The treatment must not be in combination with any of the following: (i) abemaciclib, (ii) pembrolizumab</i>					
Prescribing Instructions:					
Retain all pathology imaging and investigative test results in the patient's medical records. Do not submit copies of these as part of the authority application.					
Administrative advice: Patients may qualify for PBS-subsidised treatment under this restriction once only					
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.					

Public Summary Document - November 2023 PBAC Meeting

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.

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OLAPARIB					
olaparib 150 mg tablet, 56	New 3	2	112	7 6	Lynparza
olaparib 100 mg tablet, 56	New 4	2	112	7 6	Lynparza
Restriction Summary [New 2] / Treatment of Concept [New 2A]: Authority Required					
Category / Program: GENERAL – General Schedule (Code GE)					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Indication: Adjuvant treatment of early stage breast cancer					
Treatment Phase: Continuing treatment					
Clinical criteria:					
Patient must have received previous PBS-subsidised treatment with this drug as adjuvant therapy for this condition					
AND					
Clinical criteria:					
Patient must not have developed disease recurrence while receiving treatment with this drug for this condition					
AND					
Clinical criteria:					
The treatment must not be a PBS-subsidised benefit beyond a total of 52 weeks of treatment (including any non-PBS subsidised supply)					
AND					
Clinical criteria:					
<i>The treatment must not be in combination with any of the following: (i) abemaciclib, (ii) pembrolizumab</i>					
Prescribing Instructions:					
Retain all pathology imaging and investigative test results in the patient's medical records. Do not submit copies of these as part of the authority application.					
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: 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.					

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 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.

10 Sponsor's Comment

The sponsor had no comment.