

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

1 Purpose of submission

- 1.1 This Category 2 submission requested Authority Required (telephone/online) listing for olaparib for the adjuvant treatment of human epidermal growth factor 2 negative (HER2-) high-risk¹ early breast cancer with a confirmed germline BRCA1 or BRCA2 mutation who have previously been treated with neoadjuvant or adjuvant chemotherapy.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus placebo ('watch and wait').

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

Component	Description
Population	Adult patients with BRCA-mutated HER2-negative high-risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy
Intervention	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 non-inferior safety when compared to placebo, in patients with HER2-negative high-risk early breast cancer with a confirmed BRCA1 or BRCA2 mutation

Source: Table 1.1, p6 of the submission.

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

2 Background

Registration status

- 2.1 TGA status at time of PBAC consideration: not registered for this indication.
- 2.2 TGA registration was sought for olaparib for adjuvant treatment of adult patients with BRCA-mutated (BRCA_m) HER2-negative high-risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy. The TGA

¹ eBC with a high risk of recurrence is defined as any of the following:

- Triple negative breast cancer patient who had received prior neoadjuvant chemotherapy must have had residual invasive cancer in the breast and/or resected lymph nodes,
- Hormone receptor positive, HER2-negative, patient who had received prior neoadjuvant chemotherapy must have had residual invasive cancer in the breast and/or resected lymph nodes,
- Triple negative breast cancer patient who had received prior adjuvant chemotherapy must have had node positive disease or primary tumour greater than 20 mm, or
- Hormone receptor positive, HER2-negative, patient who had received prior adjuvant chemotherapy must have had 4 or more positive lymph nodes.

- Delegate’s Overview was provided with the pre-PBAC response, and stated that the benefit-risk balance in high-risk *gBRCAm* eBC was considered positive.
- 2.3 Olaparib is TGA approved for indications in metastatic breast cancer, ovarian cancer, adenocarcinoma of the pancreas, and prostate cancer.
 - 2.4 The TGA clinical evaluation report rounds 1 and 2 were available. The TGA evaluator noted that that overall survival (OS) data from the key trial was only 8% mature, and proposed that providing final OS data, when available, should be a condition of approval (TGA Clinical evaluation report for olaparib (Lynparza) Round 2).
 - 2.5 This was a streamlined codependent submission with a requested MBS item for germline variant testing to determine the presence of *BRCA1* or *BRCA2* pathogenic/likely pathogenic gene variants in patients with triple negative early breast cancer or hormone receptor positive, HER2-negative , early breast cancer with high-risk characteristics.
 - 2.6 The MSAC executive determined that a streamlined co-dependent pathway was appropriate. The application was scheduled for MSAC consideration at its March 2023 meeting. The requested MBS item is shown in Table 2.

Table 2: Requested MBS item descriptors (MSAC Application 1716)

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, (iv) high recurrence score (multigene assay), requested by a specialist or consultant physician, to determine eligibility for olaparib under the Pharmaceutical Benefits Scheme (PBS)	
Maximum one test per lifetime	
Fee: \$1,200.00 Benefit: 75% = \$900.00 85% = \$1,112.10	
Explanatory notes Patients who are found to have a pathogenic or likely pathogenic variant in <i>BRCA1</i> or <i>BRCA2</i> 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 1.7, p30 of the submission.

BRCA = breast cancer gene, *HER2* = human epidermal growth factors receptor 2, MBS = Medicare Benefits Schedule.

De novo metastatic disease:

- 2.7 Patients with de novo metastatic disease (roughly 5% to 15% of *BRCA*-positive patients in Australia) would not be able to access olaparib under the proposed listing, which may raise equity concerns. The Economics Sub Committee (ESC) noted that the sponsor had not submitted a PBAC application for this indication to date and that cost-effectiveness had not been assessed in this population.
- 2.8 The ESC noted that the phase III OlympiAD trial compared olaparib monotherapy with standard therapy in patients with *gBRCA* mutation and HER2–negative metastatic breast cancer. OlympiAD reported a statistically significant benefit in the primary

outcome of PFS for olaparib (n=205) vs single-agent capecitabine, eribulin or vinorelbine (n=97)(median: 7.0 months vs 4.2 months, HR=0.58 (95% CI: 0.43, 0.80)), but the final result for OS (64% maturity, 25 months FU) was not statistically significant (median: 19.3 months vs 17.1 months, HR=0.90 (95% CI: 0.66, 1.23). Cross-over was not part of the study protocol; 8 of 97 patients in the chemotherapy arm had subsequent (off-study) PARPi treatment. The ESC considered that the pre-planned subgroup analysis of OS for patients who had not received chemotherapy for metastatic disease (n=78) in the phase III OlympiAD trial suggests a potential survival advantage (HR=0.51, 0.29, 0.90), but considered potential confounding, small sample size and lack of statistically significant OS advantage in the overall population limits interpretation.

- 2.9 The Pre-Sub-Committee Response (PSCR) estimated < 500 to < 500 incident cases per year over the next six years diagnosed as Stage IV BC based on AIHW estimates of patients. The PSCR assumed that at least 95% of eligible de novo mBC patients would elect treatment, which resulted in an estimate of < 500 to < 500 patients treated with olaparib per year. The PSCR stated that the sponsor currently provides olaparib treatment as a part-paid patient access program for patients with de novo and late stage metastatic HER2-negative breast cancer with confirmed germline *BRCA1* and/or *BRCA2* mutation. The ESC considered that the potential uptake of olaparib over other agents that are currently available for metastatic breast cancer was unclear. The pre-PBAC response stated that based on clinical advice, the estimated number of de novo mBC patients provided in the PSCR (up to < 500 incident patients per year) may be an underestimate and that a detailed analysis of the literature may be required.
- 2.10 With regard to *BRCA* testing, the PSCR estimated that up to 500 to < 5000 de novo mBC patients would need to be tested for *gBRCAm* prior to olaparib treatment, based on an assumption that a new MBS item for germline *BRCA* mutation test in HER2-negative de novo mBC would be used, with use limited to patients with Stage IV de novo mBC at diagnosis, with HER2-negative disease and 80% to 95% of these patients taking up the *gBRCA* test. These estimates had not been independently verified.

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

3 Requested listing

- 3.1 The proposed restriction is shown below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OLAPARIB						
olaparib 150 mg tablet, 56	New	Published: \$6,630.78 Effective: \$█	2	112	5 (initial) 6 (<i>continuing</i>)	Lynparza
olaparib 100 mg tablet, 56	New	Published: \$6,630.78 Effective: \$█	2	112	5 (initial) 6 (<i>continuing</i>)	Lynparza

Public Summary Document – March 2023 PBAC Meeting

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)
Indication: Adjuvant treatment of early stage breast cancer
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.
Treatment Phase: Initial treatment
Clinical criteria:
The condition must be each of: (i) negative for human epidermal growth factor receptor 2 (HER2) overexpression, (ii) hormone receptor positive, (iii) early stage disease (i.e. the most recent medical imaging indicates an absence of disease metastasis); or
The condition must be each of: (i) negative for human epidermal growth factor receptor 2 (HER2) overexpression, (ii) negative for hormone receptor status, (iii) early stage disease (i.e. the most recent medical imaging indicates an absence of disease metastasis)
AND
Clinical criteria:
Patient should have to has completed at least six cycles (or experienced toxicity necessitating withdrawal) of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or both agents.
AND
The treatment must be adjuvant to surgical resection
AND
The condition must be associated with a class 4 or 5 <i>BRCA1</i> or <i>BRCA2</i> gene mutation
AND
Clinical criteria:
The condition must be considered to be of high risk of recurrence at treatment initiation with this drug, with high risk being any of:
(i) Triple negative breast cancer patient who had received prior neoadjuvant chemotherapy must have had residual invasive cancer in the breast and/or resected lymph nodes.
(ii) Hormone receptor positive, HER2-negative, patient who had received prior neoadjuvant chemotherapy must have had residual invasive cancer in the breast and/or resected lymph nodes.
(iii) Triple negative breast cancer patient who had received prior adjuvant chemotherapy must have had node positive disease or primary tumour greater than 20 mm,
(iv) Hormone receptor positive, HER2-negative, patient who had received prior adjuvant chemotherapy must have had 4 or more positive lymph nodes
AND
Clinical criteria:
The treatment must not be a PBS-subsidised benefit beyond whichever comes first: (i) week a total of 52 weeks of treatment in accordance with the Product Information (including any non-PBS subsidised supply), (ii) disease recurrence/progression
Clinical criteria:
Patients with hormone receptor positive, HER2-negative disease must be undergoing concurrent treatment with endocrine therapy; <i>Patients with hormone receptor negative disease must be treated with olaparib monotherapy.</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.
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 progression 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) week a total of 52 weeks of treatment in accordance with the Product Information (including any non-PBS subsidised supply), (ii) disease recurrence/progression
Clinical criteria:
Patient with hormone receptor positive, HER2-negative disease must be undergoing concurrent treatment with endocrine therapy
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.

- 3.2 The submission 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. The 100 mg strength would be used for dose reductions.
- 3.3 The proposed PBS listing required hormone receptor positive patients to be undergoing concurrent treatment with endocrine therapy (ET). This was not required in the proposed TGA indication. In the key olaparib trial (OlympiA) ET was to be given in HR+ patients according to institutional guidelines, and the proportion of HR+ patients treated with ET was 89.5% (see paragraph 6.11). The ESC considered it feasible that some HR+ patients may not be appropriate for ET.
- 3.4 The OlympiA trial required that patients complete 6 cycles of chemotherapy before commencing olaparib. The proposed listing would allow patients to receive olaparib if they are unable to complete six cycles of chemotherapy due to toxicity or intolerance requiring withdrawal. The PSCR reiterated that clinicians have requested that patients should not be excluded where they do not complete chemotherapy treatment due to reasons including, but not limited to, toxicity necessitating withdrawal or development of an intolerance whilst on chemotherapy (containing anthracyclines, taxanes or both agents). The PBAC and ESC agreed with the rationale in the submission and PSCR that requiring 6 cycles of chemotherapy would not be appropriate in clinical practice as patients may not be able to complete chemotherapy due to toxicity or intolerance.
- 3.5 The washout period for systemic chemotherapy prior to randomisation in the OlympiA trial was 3 weeks with patients ideally being randomised within 8 weeks of completion

- of their last treatment (surgery, chemotherapy, or radiotherapy), but in no case longer than 12 weeks.
- 3.6 The trial excluded patients who had undergone any previous treatment with a PARP inhibitor, including olaparib. This exclusion is not present in the requested PBS listing. The current PBS listing for 1L treatment of high grade stage III/IV ovarian cancer does not permit prior treatment with a PARP inhibitor. Patients treated for eBC with adjuvant olaparib may be ineligible for treatment with a PARP inhibitor should they subsequently develop ovarian cancer.
 - 3.7 The trial only recruited patients with an ECOG performance status of 0 to 1. This limitation was not included in the proposed listing.
 - 3.8 The draft Product Information (PI) recommends that patients are treated for a maximum of 1 year, or until disease recurrence, whichever occurs first. The requested listing provides 1,344 tablets across the initial and continuing treatment restrictions. This is not enough to complete a 1-year course of olaparib as it only covers 336 days. Seven repeats for the continuing phase would provide a treatment duration closer to 365 days of treatment without the prescriber having to write a third prescription.
 - 3.9 The submission stated that the sponsor would provide compassionate access to adjuvant olaparib treatment for patients who meet the proposed PBS criteria and estimated approximately < 500 patients would require transitioning to PBS-subsidised supply (i.e. 'grandfather' arrangements) if PBS listed as proposed. The submission assumed that a separate grandfather restriction will not be required as these patients will meet the initial treatment criteria. The Secretariat advised that the intent of its suggested changes was to have a single restriction that is silent on 'Treatment phase', otherwise a treatment phase description of 'Initial treatment' is potentially confusing for prescribers as 'grandfather' patients are technically 'continuing treatment' as opposed to initiating treatment. Initiating patients by nature would meet the criterion about not exceeding 52 weeks of treatment, while for continuing patients and 'grandfather' patients, the prescriber would need to be mindful of the number of repeats prescribed, as well as observing if any disease recurrence has occurred or not. A justification for having several treatment phases may be that for continuing treatment, it would be easier in practice for prescribers to not have to reaffirm clinical findings that have been made with the initial authority and which do not change over time.
 - 3.10 The sponsor requested a special pricing arrangement (SPA) for olaparib for the treatment of *BRCAM*, HER2-negative, early breast cancer (eBC). The effective price (DPMQ \$, 112 tablets) is consistent with the existing SPA for olaparib in *BRCA*-positive ovarian cancer. The ESC noted that while the requested effective AEMP in the current submission (\$, 112 tablets) was consistent with the *BRCAM* ovarian cancer indication (effective AEMP \$, 112 tablets), it was higher than the effective price for olaparib in other indications considered by the PBAC more recently, including castration resistant

metastatic carcinoma of the prostate recommended in November 2021 (effective AEMP \$112 tablets).

3.11 The ESC noted that the submission requested the same price for the proposed listing as the current listing for olaparib in BRCA-positive ovarian cancer, however this did not appear to be justified by the clinical evidence in the submission. For example, the ESC noted that the absolute benefit on OS for newly diagnosed BRCA-positive ovarian cancer is much larger than the corresponding benefit in early gBRCA-positive breast cancer. Specifically, ovarian cancer derived from the PAOLA-1 study²: Five-year OS was: 73.2% in the olaparib+bevacizumab group vs 53.8% (delta 19.4%); early breast cancer derived from the OlympiA trial as reported by Geyer et al (2022)³: Four-year OS was 89.8% in the olaparib-group and 86.4% in the placebo-group (delta 3.4%, 95% CI -0.1% to 6.8%).

3.12 The PBAC noted the following concerns:

- The proposed PBS criteria could be simplified by deleting the first two proposed clinical criteria (shown below) and replacing them with the proposed simplified wording (also shown below).

1	The condition must be each of: (i) negative for human epidermal growth factor receptor 2 (HER2) overexpression, (ii) hormone receptor positive, (iii) early stage disease (i.e. the most recent medical imaging indicates an absence of disease metastasis); or
2	The condition must be each of: (i) negative for human epidermal growth factor receptor 2 (HER2) overexpression, (ii) negative for hormone receptor status, (iii) early stage disease (i.e. the most recent medical imaging indicates an absence of disease metastasis)
Simplified	The condition must be negative for human epidermal growth factor receptor 2 (HER2) overexpression

- The patient should not be required to have completed six cycles of chemotherapy as discussed in paragraph 3.4, therefore the following proposed criterion should be deleted.

3	Patient should have to has completed at least six cycles (or experienced toxicity necessitating withdrawal) of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or both agents.
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- The proposed PBS criteria could be simplified with respect to the patients at high risk of recurrence, as follows.

² LBA29 - Final overall survival (OS) results from the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib (ola) plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (AOC). *Annals of Oncology* (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089. <https://oncologypro.esmo.org/meeting-resources/esmo-congress/final-overall-survival-os-results-from-the-phase-iii-paola-1-engot-ov25-trial-evaluating-maintenance-olaparib-ola-plus-bevacizumab-bev-in-pat>

³ Geyer CE. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in *BRCA1/2* and high-risk, early breast cancer. *Ann Oncol*. 2022 Dec;33(12):1250-1268. doi: 10.1016/j.annonc.2022.09.159. Epub 2022 Oct 10. PMID: 36228963.

Prescribing instructions:

For the first PBS authority application only, where applicable, confirm the following:

- 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, confirm that the patient has at least 4 positive lymph nodes.

- Add a new criterion consistent with the trial, that olaparib must be commenced within 12 weeks of completing other therapy, noting this could include surgery, radiotherapy or chemotherapy (see paragraph 3.5).
- The continuing restriction should be revised to refer to recurrence (not progression): as follows: ‘Patient must not have developed disease recurrence while receiving treatment with this drug for this condition’.
- In both initial and continuing restrictions, it is not necessary to specify that endocrine therapy must be used for HR+ patients
- If olaparib is PBS listed in eBC, it may be appropriate to clarify in the current PBS listings for PARPi 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 (ovarian cancer; see paragraph 3.6).
- Combination use of pembrolizumab (see paragraph 5.3) and olaparib (for patients with *BRCAm* breast cancer) would not be appropriate as this combination is unlikely to be cost-effective and there is a lack of safety and efficacy data to support it. Therefore, the restrictions should prevent combination use of olaparib and pembrolizumab.

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%⁴. 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 growth factor receptor 2 (HER2)⁵. Cancers that do not express these disease modifiers are called 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 recurrence⁶. A

⁴ Health, A. I. o. and Welfare (2021). Cancer in Australia 2021. Canberra, AIHW.

⁵ Pourzand, A., M. B. Fakhree, S. Hashemzadeh, M. Halimi and A. Daryani (2011). "Hormone receptor status in breast cancer and its relation to age and other prognostic factors." *Breast Cancer (Auckl)* 5: 87-92.

⁶ Diana, A., F. Carlino, E. Franzese, O. Oikonomidou, C. Criscitiello, F. De Vita, F. Ciardiello and M. Orditura (2020). "Early Triple Negative Breast Cancer: Conventional Treatment and Emerging Therapeutic Landscapes." *Cancers (Basel)* 12(4)

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 recurrence⁷.

- 4.2 *BRCA* mutations, as well as the criteria to determine patients at high-risk detailed in the proposed restriction⁸, cause increased rates of disease recurrence in TNBC and HR+ early breast cancer patients. There remains an unmet need for therapies that prevent or delay disease recurrence in these populations.
- 4.3 Current clinical management after initial treatment in HER2-negative, *BRCAm* tumours, in high-risk early breast cancer patients, is monitoring for disease recurrence, or 'watch and wait'. The patients in the key trial and in the proposed restriction can be further classified as HR+ or TNBC (HER2-, HR-). ET is given in patients with HR-positive cancers (i.e. not for TNBC patients), but no other specific guidelines or recommendations exist⁹. The clinical management algorithm would change by introducing testing for germline *BRCA* 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 *BRCA* mutated patients to be eligible for adjuvant olaparib for 1 year or until disease progression. The ESC considered the place in therapy described by the submission was appropriate.
- 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 already have issues with DNA repair, such as *BRCA* mutated cancers which lack functional components of the homologous recombination repair pathway¹⁰.

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

⁷ 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.

⁸ eBC with a high risk of recurrence is defined as any of the following:

- a) Triple negative breast cancer patient who had received prior neoadjuvant chemotherapy must have had residual invasive cancer in the breast and/or resected lymph nodes,
- b) Hormone receptor positive, HER2-negative, patient who had received prior neoadjuvant chemotherapy must have had residual invasive cancer in the breast and/or resected lymph nodes,
- c) Triple negative breast cancer patient who had received prior adjuvant chemotherapy must have had node positive disease or primary tumour greater than 20 mm, or
- d) Hormone receptor positive, HER2-negative, patient who had received prior adjuvant chemotherapy must have had 4 or more positive lymph nodes.

⁹ 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

¹⁰ Goulooze, S. C., A. F. Cohen and R. Rissmann (2016). "Olaparib." *Br J Clin Pharmacol* 81(1): 171-173.

5 Comparator

- 5.1 The submission nominated placebo ('watch and wait') as the main comparator. There are currently no specific guidelines for the management of *BRCA* mutated, HER2-negative, high-risk, eBC patients after initial therapy has been completed. As such, most patients undergo monitoring for disease recurrence. Hormone receptor positive patients will receive ongoing ET which can be combined with olaparib. The ESC considered the nominated comparator was appropriate.
- 5.2 The commentary noted there is evidence for the efficacy of capecitabine¹¹ and abemaciclib¹² in high-risk eBC patients and raised these as potential comparators. However, no trials have been carried out specifically looking at these compounds in HER2-negative, *BRCA* mutated, eBC patients and so an accurate comparison is not currently possible. The PBAC noted that capecitabine is used in clinical practice for TNBC patients, however concomitant capecitabine was not allowed in the OlympiA trial.
- 5.3 The PBAC considered two other submissions for medicines in early breast cancer at the March 2023 meeting (one for abemaciclib and one for pembrolizumab)¹³. The PBAC considered there may be some overlap in patient populations of the medicines being considered for early breast cancer, however this would be less relevant to olaparib because it would be the preferred agent for *gBRCAm* patients in eBC if PBS listed.

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 (13), and organisations (5) via the Consumer Comments facility on the PBS website. The comments from individuals 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

¹¹ Masuda, N., S.-J. Lee, S. Ohtani, Y.-H. Im, E.-S. Lee, I. Yokota, K. Kuroi, S.-A. Im, B.-W. Park, S.-B. Kim, Y. Yanagita, S. Ohno, S. Takao, K. Aogi, H. Iwata, J. Jeong, A. Kim, K.-H. Park, H. Sasano, Y. Ohashi and M. Toi (2017). "Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy." *New England Journal of Medicine* 376(22): 2147-2159.

¹² Johnston, S. R. D., N. Harbeck, R. Hegg, M. Toi, M. Martin, Z. M. Shao, Q. Y. Zhang, J. L. Martinez Rodriguez, M. Campone, E. Hamilton, J. Sohn, V. Guarneri, M. Okada, F. Boyle, P. Neven, J. Cortés, J. Huober, A. Wardley, S. M. Tolaney, I. Cicin, I. C. Smith, M. Frenzel, D. Headley, R. Wei, B. San Antonio, M. Hulstijn, J. Cox, J. O'Shaughnessy and P. Rastogi (2020). "Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE)." *J Clin Oncol* 38(34): 3987-3998

¹³ <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/agenda/pdf/2022/PBAC-meeting-agenda-March-2023-v2.pdf>, accessed 13 Jan 2023.

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 The Medical Oncology Group of Australia (MOGA) 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 A¹⁴, which is the highest grade of the ESMO-MCBS in the curative setting, based on a comparison with placebo.
- 6.4 The PBAC noted and welcomed input from Pink Hope in support of the olaparib listing. The PBAC noted the high clinical need for patients with *BRCA* mutations and the impact of the disease on patients including fear of recurrence and reduced survival. The comments also noted that there are known side effects of olaparib including nausea, fatigue, anaemia, vomiting, and headache which are common side effects of many cancer treatments and there is an option for prescribers to reduce the dose of olaparib if necessary due to side effects.
- 6.5 The PBAC noted and welcomed input from Breast Cancer Network Australia (BCNA) which supported the proposed listing on the basis of the OlympiA trial. The letter described that patients with *BRCAm* breast cancer have often had a devastating experience of breast cancer in their family, and that the proposed PBS listing would be of great benefit to these patients. As well as improved survival they 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 *BRCA* testing and PBS listing for the drug there would be inequitable access to treatment and the benefits would only be available to those who could self-fund.
- 6.6 The PBAC also noted and welcomed the input from Rare Cancers Australia which supported the proposed listing.

Clinical trials

- 6.7 The submission was based on one head-to-head trial comparing olaparib to placebo (n=1836), the OlympiA trial. Details of this trial are provided in Table 3.

¹⁴ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017.

Table 3: Trials and associated reports presented in the submission

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
	Anonymous. Adjuvant Olaparib Improves Disease-Free Survival in Early, High-Risk, <i>BRCA</i> Mutated, HER2- Breast Cancer.	Oncologist. 2021;26 Suppl 3:S3-S4
OlympiA NCT02032823	A. N. James Tutt, B. Kaufman, R. D. Gelber, E. Mc Fadden, C. D. Goessl, G. Viale, A. Arahmani, D. Fumagalli, H. A. Azim, W. Wu, A. Grochulewicz, J. P. Costantino, P. Rastogi, J. E. Garber and C. E. Geyer. 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 (<i>gBRCAm</i>).	Journal of Clinical Oncology. Conference. 2015;33(15 SUPPL. 1)
	A. Tutt, J. E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R. D. Gelber, E. De Azambuja, A. Fielding, J. B. Gelpi, K. A. Gelmon, N. Baker, A. Arahmani, E. Senkus-Konefka, E. Mc Fadden, V. Karantza, S. R. Lakhani, G. Yothers, C. Campbell and C. E. Geyer. 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, G. Viale, D. Fumagalli, P. Rastogi, R. D. Gelber, E. de Azambuja, A. Fielding, Balmana, J., S. M. Domchek, K. A. Gelmon, S. J. Hollingsworth, L. A. Korde, B. Linderholm, H. Bandos, E. Senkus, J. M. Suga, Z. Shao, A. W. Pippas, Z. Nowecki, T. Huzarski, P. A. Ganz, P. C. Lucas, N. Baker, S. Loibl, R. McConnell, M. Piccart, R. Schmutzler, G. G. Steger, J. P. Costantino, A. Arahmani, N. Wolmark, E. McFadden, V. Karantza, S. R. Lakhani, G. Yothers, C. Campbell, C. E. Geyer,. Adjuvant Olaparib for Patients with <i>BRCA1</i> - or <i>BRCA2</i> -Mutated Breast Cancer.	New England Journal of Medicine. 2021;Vol.384(25):2394-2405p

Trial ID	Protocol title/ Publication title	Publication citation
	A. N. J. Tutt, J. Garber, R. D. Gelber, K. A. Phillips, A. Eisen, O. T. Johannsson, P. Rastogi, K. Y. Cui, S. A. Im, R. Yerushalmi, A. M. Brufsky, M. Taboada, G. Rossi, G. Yothers, C. Singer, L. E. Fein, N. Loman, D. Cameron, C. Campbell and C. E. Geyer. 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 (g <i>BRCAm</i>) associated breast cancer.	Annals of Oncology. 2022;Vol.33(5):566-568p

Source: Table 2.3, p38 of the submission.

6.8 The key features of the direct randomised trial are summarised in Table 4.

Table 4: 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 ¹⁵ previously treated with chemotherapy.	Primary outcome: IDFS. Secondary outcomes: OS, DDFS, FACIT- Fatigue, EORTC QLQ-C30, safety.	IDFS EORTC QLQ-C30

Source: Figure 2.2, p41, table 2.4, pp43-44, table 2.8 pp50-54, table 2.14, pp64-66, table 2.11, p58 of the submission.

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, IDFS = invasive disease-free survival, MC = multi-centre, OS = overall survival, PC = placebo controlled, QLQ-C30 = quality of life questionnaire core 30, R = randomised.

- 6.9 The primary outcome of invasive disease-free survival (IDFS) is defined in the submission as ‘The time from randomisation to date of first recurrence, where recurrence is defined as loco-regional, distant recurrence, new cancer or death from any cause’. The median IDFS had yet to be reached at data cut-off 2 (DCO2) 12 July 2021.
- 6.10 Initially the OlympiA trial only included TNBC patients. Approximately 18 months after the trial had begun, an amendment to the protocol was made to include HR+, HER2-eBC patients. As a result TNBC patients make up the majority of the trial population (82.3% TNBC and 17.7% HR+ HER2-). In comparison, the submission estimated TNBC in the Australian eBC population to be between 12-24%. The ESC noted this estimate may not be applicable to the proposed PBS population (see paragraph 6.16).
- 6.11 The trial protocol allowed concurrent ET for patients who were HR+ (including ER and/or PgR positive). 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.

¹⁵ Patients could be positive or negative for hormone receptors. This was a stratification factor during randomisation.

Comparative effectiveness

- 6.12 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. The results of IDFS from the OlympiA trial are shown in Table 5. The olaparib arm of the trial showed a statistically significant reduction in IDFS events when compared to placebo at a median follow-up of 3.5 years (14.5% in olaparib, 22.6% in placebo, hazard ratio 0.63 (95% CI 0.50, 0.78) at DCO2). The Kaplan-Meier curves for IDFS in the OlympiA trial are presented in Figure 1.
- 6.13 Secondary outcomes included OS and distant disease-free recurrence. The OS data were immature at DCO2 (75 (8.1%) deaths in olaparib and 109 (11.9%) deaths in placebo at a median follow-up of 3.5 years) owing to the long survival seen in eBC patients. The submission stated that the deaths observed in the OlympiA trial were from 'early progressors' and the likely full extent of OS gain has not been realised and likely will not be observed for many years after the trial has concluded. The OS results from the OlympiA trial are displayed in Table 5. At DCO2 (median follow-up 3.5 years), there was a statistically significant difference in OS (hazard ratio 0.68 (98.5% CI 0.47, 0.97)). The 98.5% CI for the HR at DCO2 was reported to be inferential, according to the alpha spending rules for the DCO2 interim analysis of OS. The median OS had not been reached. The Kaplan-Meier curves for OS in the OlympiA trial are presented in Figure 2.
- 6.14 The submission noted that TNBC is associated with a faster rate of disease recurrence (typically within 5 years) compared with HR-positive, HER2-negative breast cancer (typically over 20 years up to a lifetime), as reported by Sopik et al. 2019¹⁶. As such, long term survival data available for the HR-positive population in OlympiA is immature when compared to the TNBC population.
- 6.15 The distant disease-free survival (DDFS) data from the OlympiA trial are also presented in Table 5 and these findings align with the results 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. This was a statistically significant difference (hazard ratio 0.61 (95% CI 0.48, 0.77)).

¹⁶ Sopik V, Sun P, Narod SA. Predictors of time to death after distant recurrence in breast cancer patients. *Breast Cancer Research and Treatment*. 2019;173(2):465-74.

Table 5: Results of key outcomes in the OlympiA trial DCO2 (median follow up of 3.5 years)

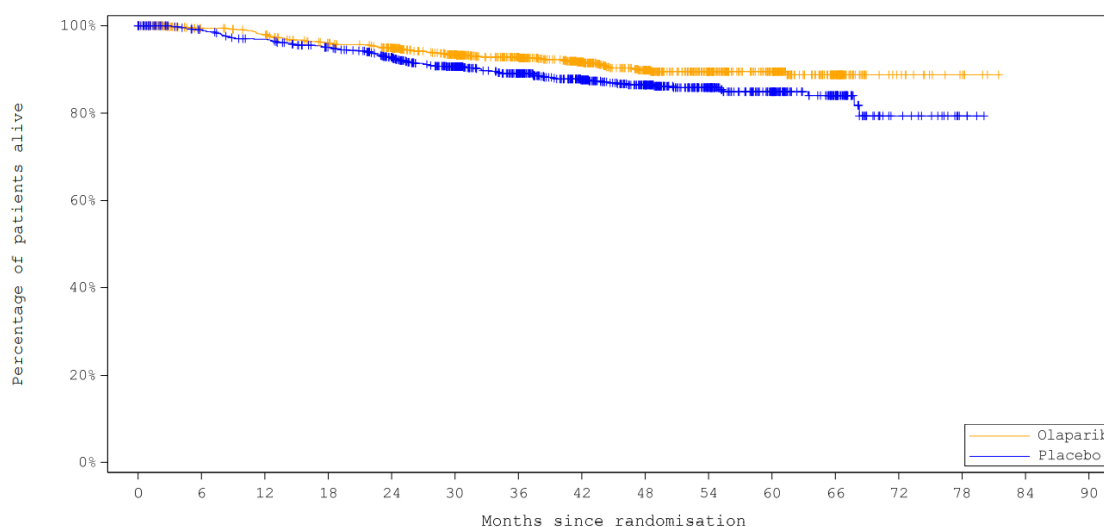
Outcome	Events		Hazard ratio (95% CI) ^a	Median time to event
	Olaparib n/N (%)	Placebo n/N (%)		
IDFS	134 /921 (14.5%)	207/ 915 (22.6%)	0.63 (0.50, 0.78)	NR
OS	75/921 (8.1%)	109/ 915 (11.9%)	0.68 (0.50, 0.91)	NR
DDFS	107/921 (11.6%)	172/ 915 (18.8%)	0.61 (0.48, 0.77)	NR

a. Submission reported that 95% CI 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)).

Source: Table 2.16, p68, table 2.17, p69, and table 2.18, p71 of the submission), Table 14.2.7 (DCO2 addendum part b).

CI = confidence interval, 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** indicates statistically significant results.

Figure 1: Kaplan-Meier Plot for IDFS (ITT Population) in OlympiA at median follow-up of 3.5 and 3.6 years (olaparib and placebo respectively)

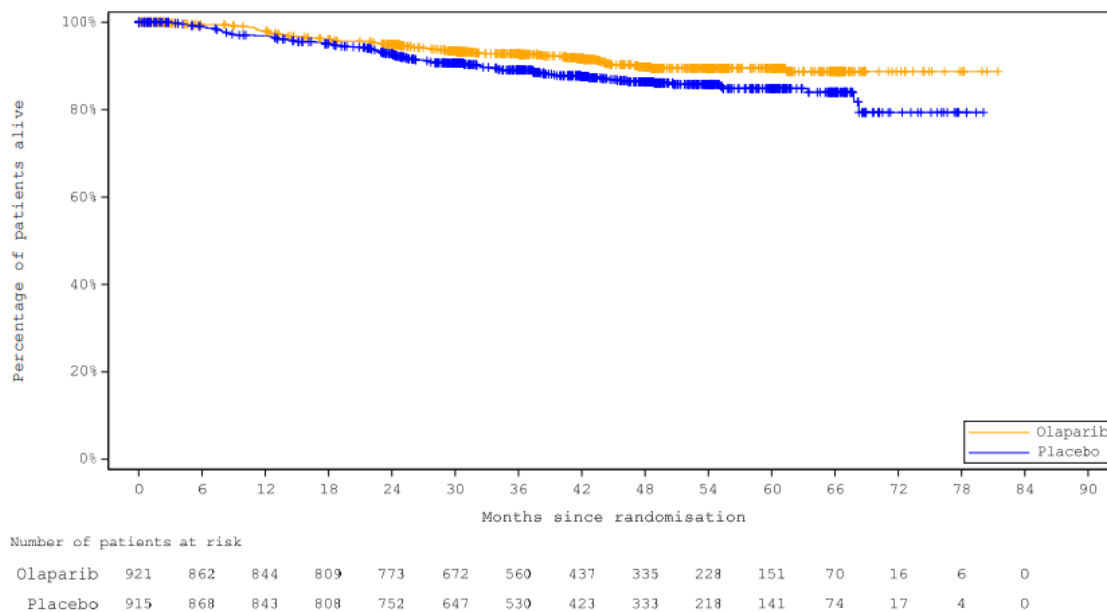


Number of patients at risk		0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
Olaparib	921	862	844	809	773	672	560	437	335	228	151	70	16	6	0		
Placebo	915	868	843	808	752	647	530	423	333	218	141	74	17	4	0		

Source: Figure 2.3, p68 of the submission.

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

Figure 2: Kaplan-Meier Plot for OS (ITT Population) in OlympiA at median follow-up of 3.5 and 3.6 years



Source: Figure 2.5, p71 of the submission.
ITT = intention to treat, OS = overall survival.

Subgroup analyses

- 6.16 Hormone receptor status was a stratification factor in the OlympiA trial, which included a smaller proportion of HR-positive, HER2-negative patients (17.7%) compared to the TNBC population (82.3%). In contrast, the submission estimated the proportion of HR-positive, HER2-negative patients in Australian clinical practice is estimated to be approximately 56.9 to 79.6% compared with 12 to 24% for TNBC. The ESC noted that the submission’s estimates were drawn from Australian studies (Bartlett 2021¹⁷ and Naher 2018¹⁸) in broader patient populations that were not limited to those with *gBRCA* mutations, and therefore may not be applicable to the proposed PBS population.
- 6.17 Given the differences in the relative proportion of HR+, HER2- patients compared to TNBC patients in the OlympiA (82.3% TNBC and 17.7% HR+ HER2-) trial compared with the Australian population (12-24% TNBC and 56.9-79.6% HR+ HER2-), the submission presented subgroup analyses to assess the consistency of treatment effect across HR status (HR+ HER2- versus TNBC). Subgroup analyses by HR status are summarised in Table 6. In the OlympiA trial, 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

¹⁷ Bartlett M, Beral V, Dolja-Gore X, Gathani T, Liu B. Detailed breast cancer pathology data for large-scale studies – access and completeness in NSW, Australia. Public Health Research & Practice.

¹⁸ Naher S, Tognela A, Moylan E, Adams DH, Kiely BE. Patterns of care and outcomes among triple-negative early breast cancer patients in South Western Sydney. Internal Medicine Journal. 2018 May;48(5):567-72.

across subgroups, the test for interaction was not statistically powered. As TNBC patients are potentially over-represented in the OlympiA trial in comparison to the Australian setting, this may overestimate the effectiveness of olaparib.

- 6.18 The hazard ratios between the HR+, HER2- population and the TNBC population are largely similar for IDFS (0.68 vs 0.62, respectively) and DDFS (0.69 vs 0.59, respectively), but less similar for OS (0.90 vs 0.64, respectively) as shown in Table 6. Note that the event rate for OS was low across both treatment arms for the HR+, HER2- population (n=16 events in the olaparib arm vs n=17 events in the placebo arm), thereby increasing the confidence interval.
- 6.19 The PSCR stated that olaparib has an established mechanism of action that targets *BRCA* mutations and as such, is expected to be similarly efficacious in all patients with *BRCA* mutations. ESC noted that there was no statistical evidence of treatment-effect modification by TNBC vs HR-positive, but that OlympiA was not statistically powered for such a comparison.

Table 6: Comparison of IDFS, DDFS and OS by HR status in OlympiA at DCO2

HR status	Events		Hazard ratio (95% CI)	Interaction p-value
	Olaparib n/N (%)	Placebo n/N (%)		
IDFS				
HR-positive, HER2-negative	25/168 (14.9%)	34/157 (21.7%)	0.68 (0.40, 1.13)	0.754
TNBC	109/751 (14.5%)	173/758 (22.8%)	0.62 (0.49, 0.79)	
DDFS				
HR-positive, HER2-negative	23/168 (13.7%)	31/157 (19.7%)	0.69 (0.40, 1.18)	0.608
TNBC	84/751 (11.2%)	141/758 (18.6%)	0.59 (0.45, 0.77)	
OS				
HR-positive, HER2-negative	16/168 (9.5%)	17/157 (10.8%)	0.90 (0.450, 1.78)	0.381
TNBC	59/751 (7.9%)	92/758 (12.1%)	0.64 (0.46, 0.88)	

Source: Table 2.32, p 91 of the submission.

CI = confidence interval; DDFS = distance disease-free survival; HER2 = human epidermal receptor 2; HR = hormone receptor; IDFS = invasive disease-free survival; N = number; OS = overall survival; TNBC = triple negative breast cancer.

Bold indicates a statistically significant result.

- 6.20 The type of chemotherapy patients received (neoadjuvant or adjuvant) was 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). Table 7 presents the chemotherapy subgroup analysis for IDFS, DDFS, and OS.
- 6.21 For IDFS, the results were similar across the adjuvant and neoadjuvant subgroups. Although the results for OS and DDFS were slightly different across subgroups, the differences were not statistically significant and there was no consistent trend in favour of either subgroup.

Table 7: Comparison of IDFS, DDFS, and OS by adjuvant or neoadjuvant chemotherapy in OlympiA at DCO2

Prior chemotherapy	Events		Hazard ratio (95% CI)	Interaction p-value
	Olaparib n/N (%)	Placebo n/N (%)		
IDFS				
Adjuvant	46/461 (10.0%)	75/455 (16.5%)	0.618 (0.425, 0.888)	0.763
Neoadjuvant	88/460 (19.1%)	132/460 (28.7%)	0.622 (0.473, 0.813)	
OS				
Adjuvant	22/461 (4.8%)	28/455 (6.2%)	0.783 (0.444, 1.365)	0.753
Neoadjuvant	53/460 (11.5%)	81/460 (17.6%)	0.638 (0.449, 0.900)	
DDFS				
Adjuvant	33/461 (7.2%)	59/455 (13.0%)	0.562 (0.363, 0.855)	0.583
Neoadjuvant	74/460 (16.1%)	113/460 (24.6%)	0.623 (0.463, 0.832)	

Source: Table 14.2.13.1, table 14.2.13.3, and table 14.2.13.5 of attachment 2.3 CSR section tables figures listing part b
 CI = confidence interval, DDFS = distant disease free survival, IDFS = invasive disease free survival, OS = overall survival, n = number of patients with outcome, N = number of patients in group. **Bold** indicates a nominally statistically significant result.

- 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. The results are presented in Table 8.
- 6.24 The neoadjuvant group saw 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.

Table 8: Change from baseline for FACIT-Fatigue Score in the OlympiA trial.

Parameter	6 months		12 months		18 months		24 months	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Patients who had completed neoadjuvant chemotherapy								
Olaparib	-1.5	-2.3, -0.8	-1.5	-2.4, -0.6	1.3	0.4, 2.2	1.6	0.7, 2.4
Placebo	-0.2	-1.0, 0.6	0.0	-0.9, 0.9	1.4	0.5, 2.3	2.0	1.1, 2.9
Difference	-1.4	-2.5, -0.2	-1.6	-2.8, -0.3	-0.1	-1.4, 1.1	-0.4	-1.7, 0.8
P-value	0.017		0.017		0.819		0.518	
Patients who had completed adjuvant chemotherapy								
Olaparib	-0.7	-1.5, 0.0	-0.8	-1.6, 0.0	0.9	0.1, 1.7	1.3	0.5, 2.1
Placebo	0.6	-0.2, 1.3	0.5	-0.3, 1.2	1.2	0.4, 2.0	1.6	0.7, 2.4
Difference	-1.3	-2.3, -0.2	-1.2	-2.4, 0.1	-0.3	-1.4, 0.8	-0.3	-1.4, 0.9
P-value	0.017		0.028		0.582		0.655	

Source: Table 2.20, p73 of the submission.

CI = confidence interval, FACIT = functional assessment of chronic illness therapy. **Bold** indicates statistically significant results
 Note: The FACIT-Fatigue scale includes 13 items asking how the patients feels regarding being energetic, tired, weak or fatigued in the past 7 days with the patient selecting one of five categories of feeling levels ranging from 'not at all' to 'very much.'. The composite score is found by summing the scores of each of the 13 items and ranges from 0-52 where a higher score indicates a better quality of life. The pre-established minimally clinically meaningful change threshold for the OlympiA trial was 3 points.

- 6.25 The results from the from the EORTC QLQ-C30 are displayed in Table 9.

6.26 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 improvements in global health/QoL scores from baseline compared with placebo at 6 and 12 months but this was not sustained at 24 months.

Table 9: Change from Baseline for EORTC QLQ-C30 global health status QoL in the OlympiA trial.

Parameter	6 months		12 months		18 months		24 months	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Patients who had completed neoadjuvant chemotherapy								
EORTC QLQ-C30 Global health status QoL								
Olaparib	-0.4	-2.2, 1.4	0.5	-1.7, 2.4	3.3	1.3, 5.3	2.3	-0.6, 5.0
Placebo	0.4	-1.4, 2.2	2.7	0.7, 4.7	4.4	2.3, 6.4	6.1	3.8, 8.4
Difference	-0.8	-3.4, 1.8	-2.2	-5.0, 0.6	-1.1	-3.9, 1.7	-3.3	-6.5, -0.1
P-value	0.55		0.12		0.45		0.04	
Patients who had completed adjuvant chemotherapy								
EORTC QLQ-C30 Global health status QoL								
Olaparib	-0.5	-2.2, 1.2	0.6	-1.1, 2.4	2.9	1.1, 4.7	4.5	2.6, 6.4
Placebo	2.2	0.6, 3.8	3.1	1.5, 4.8	5.1	3.3, 6.9	4.8	2.9, 6.7
Difference	-2.7	-5.1, -0.4	-2.5	-5.0, -0.1	-2.2	-4.8, 0.3	-0.3	-3.0, 2.4
P-value	0.02		0.04		0.09		0.83	

Source: Table 2.21 and table 2.22, p76 of the submission.

C30 = core 30 questions, CI = confidence interval, EORTC = European Organisation for Research and Treatment of Cancer, QLQ = quality of life questionnaire, QoL = quality of life. **Bold** indicates statistically significant results

Comparative harms

6.27 Comparative harms were reported from the OlympiA trial and are summarised in Table 10. At DCO2, 91.8% of patients in the olaparib arm and 83.8% of patients in the placebo arm had experienced at least one AE. A much larger difference was seen in treatment related AEs with 80.8% of patients in the olaparib and 53.1% of patients in the placebo experiencing treatment emergent adverse events (TEAEs).

6.28 AEs of grade 3 or higher were much more common with olaparib than with placebo, as seen in Table 11. Similarly, AEs that resulted in dose modification were much more common in the olaparib arm than in the placebo arm, as displayed in Table 10.

6.29 The submission claimed non-inferior safety for olaparib vs placebo. However, TEAEs occurred in 80.8% of patients receiving olaparib and 53.1% of patients receiving placebo. Grade 3 or higher AEs occurred in 24.5% of patients receiving olaparib, and 11.3% of patients receiving placebo.

Table 10: Summary of key adverse events in the trials

Trial ID	Olaparib n with event/N (%)	Placebo n with event/N (%)	RR (95% CI)
OlympiA			
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 2.23, p77 of the submission.

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.

Table 11: Most common grade 3 or higher AEs in the OlympiA trial.

Trial ID	Olaparib n with event/N (%)	Placebo n with event/N (%)	RR (95% CI)
OlympiA			
Patients with AE of CTCAE Grade ≥3	223/911 (24.5%)	102/904 (11.3%)	2.17 (1.75, 2.69)
Anaemia	79/911 (8.7%)	3/904 (0.3%)	26.13 (8.28, 82.46)
Neutrophil count decrease	45/911 (4.9%)	7/904 (0.8%)	6.38 (2.89, 14.07)
White blood cell count decrease	27/911 (3.0%)	3/904 (0.3%)	8.93 (2.72, 29.33)
Fatigue	16/911 (1.8%)	6 /904 (0.7%)	2.65 (1.04, 6.73)

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

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

- 6.30 The submission 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 submission (16-Dec-2020 to 15-Dec-2021) encompassing approximately 38,257 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. No other changes to the safety information were made.
- 6.31 As stated in the draft PI the incidence of myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) in patients treated in clinical trials with olaparib monotherapy, including long-term survival follow up, was <1.5%. The estimated cumulative of MDS/AML as reported in the Periodic Benefit-Risk Evaluation Report (January 2022) was 0.54% in patients exposed to olaparib during clinical development (i.e., including data from combination studies, investigator-sponsored studies and the MAP) (101 reports from data for 18,675 patients).

Benefits/harms

6.32 A summary of the comparative benefits and harms for olaparib versus placebo is presented in Table 12.

Table 12: Summary of comparative benefits and harms for olaparib and placebo

Events	Olaparib	Placebo	Absolute Difference	HR (95% CI)		
Benefits						
Invasive disease-free survival (median duration of follow up 3.5 years for olaparib, 3.6 years for placebo)						
Progressed, n/N (%)	134/921 (14.5)	207/915 (22.6)	8.1	0.63 (0.50, 0.78) P<0.0001		
Progression free at 12 months (%)	93.4	88.4	5.0			
Progression free at 24 months (%)	89.7	81.4	8.3			
Progression free at 36 months (%)	86.1	77.3	8.8			
Progression free at 48 months (%)	82.7	75.4	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)	3.8	0.68 (0.50, 0.91) P=0.0091		
Alive at 12 months (%)	98.0	96.9	1.1			
Alive at 24 months (%)	95.0	92.8	2.2			
Alive at 36 months (%)	92.8	89.1	3.7			
Alive at 48 months (%)	89.8	86.4	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)	7.2	0.61 (0.48, 0.77) P<0.0001		
Progression free at 12 months (%)	94.4	90.3	4.1			
Progression free at 24 months (%)	90.6	84.0	6.6			
Progression free at 36 months (%)	88.0	81.0	7.0			
Progression free at 48 months (%)	86.5	79.1	7.4			
Harms						
	Events		RR (95% CI)	Event rate/100 patients*		RD (95% CI)
	Olaparib n/N	Placebo n/N		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 2.16, p68, table 2.17, p69, and table 2.18, p71, Table 2.23, p77 of the submission. Table 14.3.2.18, p323 of the OlympiA trial CSR tfls part C

AE = adverse event, CTCAE = common terminology criteria for adverse events, CI = confidence interval, n = number of participants with event, N = total participants in group, RD = risk difference, RR = relative risk. **Bold** indicates statistically significant results.

* Median duration follow-of 3.5 years.

- 6.33 Based on the direct evidence presented in the submission, for every 100 patients treated with olaparib in comparison with placebo over a median duration of follow-up of approximately 3.5 years:
- 6.34 Approximately 8 additional patients would remain free of invasive disease.
- 6.35 Approximately 4 fewer patients would die.
- 6.36 Approximately 7 additional patients would remain free of distant recurrence.
- 6.37 Approximately 8 additional patients would experience grade 3 or higher anaemia.
- 6.38 Approximately 4 additional patients would experience grade 3 or higher neutrophil count decrease.
- 6.39 Approximately 1 to 2 patients may develop olaparib related MDS/AML over the long term.

Clinical claim

- 6.40 The submission described olaparib as superior in terms of effectiveness compared to placebo. The evaluation considered this claim was adequately supported. Statistically significant improvements were seen for IDFS, DDFS, and OS (Table 5). The key issues in relation to the claim were:
- 6.41 The claim of superiority was based on IDFS data, which does not have an established relationship with OS or a minimally clinically relevant change in this population.
- 6.42 The OS data were immature, even after 3.5 years follow-up. While OlympiA demonstrated an improvement in OS for olaparib compared with placebo, the event rates were low (8.1% for olaparib and 11.9% for placebo). The evaluation considered the OS data too immature for definitive conclusions to be drawn.
- 6.43 The median IDFS, DDFS, and OS were not reached.
- 6.44 The PSCR acknowledged that the IDFS and OS data from the OlympiA trial were immature however highlighted that after a median follow-up of 3.5 years for both outcomes, there was separation of KM curves (see Figure 1 and Figure 2) and statistically significant differences between the olaparib and placebo arms for IDFS (HR 0.63 (95% CI 0.50, 0.78)). The results for OS were HR 0.68 (95% CI 0.50, 0.91). The PSCR noted that the OlympiA trial would require a significantly longer duration of follow-up for the data to reach maturity (i.e. reach median OS).
- 6.45 The ESC considered that the superiority claim was supported based on IDFS data, while noting that OS data remained immature. The ESC noted that IDFS is a composite endpoint and although it is a clinically relevant measure by itself and has been endorsed by expert working groups, its relationship to OS and its minimally clinically important difference are not known in this population.
- 6.46 The submission described olaparib as non-inferior in terms of safety compared to placebo. This claim was not adequately supported. 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 and also the long-term risk of MDS/AML

- 6.47 The PSCR acknowledged that a greater proportion of patients in the olaparib arm experienced AEs leading to dose reductions, interruption or discontinuation, but asserted that the rate of AEs resulting in death during study treatment or 30-day safety follow-up remained balanced between both treatment groups. The ESC noted that the adverse event profile of olaparib is well characterised and that no new types of adverse events were identified in the setting of early breast cancer. The ESC also noted that MDS/AML was a concern with PARPis and agreed with the evaluation that the non-inferiority claim was not supported.
- 6.48 The PBAC considered that the claim of superior comparative effectiveness was reasonable based on the OlympiA trial.
- 6.49 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.

Economic analysis

- 6.50 The submission presented an economic evaluation based on the OlympiA trial. The type of economic evaluation was a cost-utility analysis. The key components of the economic evaluation are presented in Table 13.

Table 13: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Adjuvant olaparib vs placebo (no treatment)
Time horizon	40 years in the model base case versus a median of 3.5 years in the OlympiA trial.
Outcomes	Life years gained, quality adjusted life years gained, and disease free years gained.
Methods used to generate results	Markov model (semi-Markov with time varying transition probabilities)
Health states	Invasive disease-free survival, Non-metastatic recurrence, Early-onset metastatic recurrence, Late-onset metastatic recurrence, and Dead
Cycle length	1 month (365/12=30.417 days)
Transition probabilities	<p>The model has 7 transition probabilities. Transition probabilities are largely time varying and are calculated from survival curves.</p> <p>TP1 – IDFS to non-mBC (approx. 25% of all recurrences)</p> <ul style="list-style-type: none"> • Before 42 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. ABS life tables adjusted 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.</p>

Component	Summary
	<p>TP6 – early-onset mBC to death. OlympiA survival curve for the olaparib arm from metastatic disease to death with fitted parametric function.</p> <p>TP7 – late-onset mBC to death. Pooled survival curves from three treatments used in the metastatic setting. Each survival curve is first fitted with a parametric function.</p>
Extrapolation method	<p>The observed data for the IDFS survival curve is used until 42 months. A parametric function of best statistical fit is applied to the olaparib curve from 42 months to 60 months. The same function (despite not being the best fit) is applied to the placebo arm. This is TP1 and TP2.</p> <p>Extrapolation following 5 years occurs as a consequence of an assumed recurrence rate until 10 years, then no recurrences. This approach maintains the initial divergence of the IDFS curve for the lifetime of the model (except for the impact of background mortality, ie, TP3).</p> <p>Other survival curves (TP4, TP5, TP6 and TP7) are extrapolated using parametric functions. Each of these transition probabilities are common across the arms, therefore convergence is not required.</p> <p>Overall survival is not ‘extrapolated’. It is a product of all of the transition probabilities applied in the model.</p> <p>Approximately 80% of the life years (undiscounted) occur following the extent of trial data (79 months) in both arms. Almost 90% of the incremental life years (undiscounted) are accrued following 79 months.</p>
Health related quality of life	<p>Utilities are 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 2010¹⁹). • 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	<p>Testing costs are estimated based on the increment between the assumed current testing rate of 74% and the assumed uptake rate of 95%.</p>

Source: Generated during the evaluation.

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 ; *gBRCAm* = germline pathogenic variant in germline breast cancer gene; IDFS = invasive disease free survival; KM = Kaplan-Meier; mBC = metastatic breast cancer recurrence; non-mBC = non-metastatic breast cancer recurrence; TP = transition probability.

6.51 The average age of patients in the model is 43 years. This may be younger than the average age of patients in the Australian setting. An Australian study of patients with TNBC who are *gBRCA* mutation positive reported the average age to be 50.3 years²⁰. The model is sensitive to the starting age.

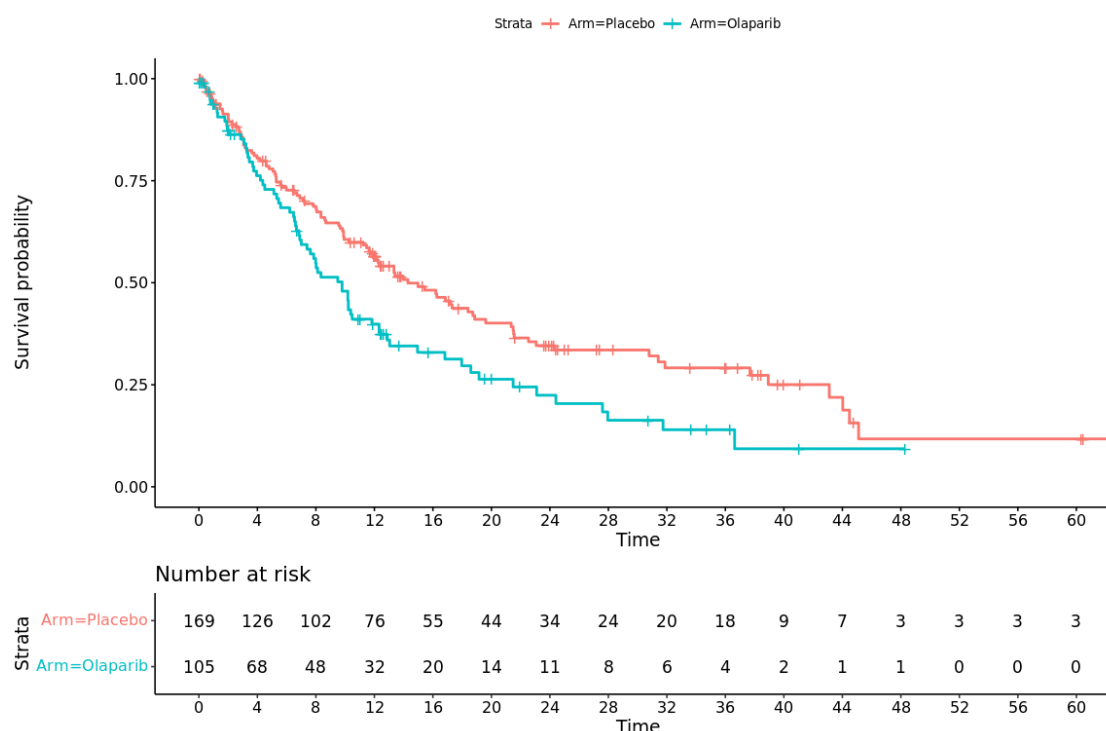
¹⁹ Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. The European journal of health economics. 2010;11(4):427-34.

²⁰ 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.

- 6.52 The model uses observed data from OlympiA, which implicitly assumes the same proportion of TNBC: HR+ patients for estimating transitions from IDFS. 82.3% of patients in OlympiA were TNBC, however the proportion of patients with *gBRCA* mutations who are TNBC in the Australian setting is unknown. As olaparib appeared to perform better in patients with TNBC (HR for OS = 0.64 95% CI 0.46, 0.88) compared with HR+ (HR for OS = 0.90 95% CI 0.45, 1.78), if the Australian setting differs from the OlympiA trial on this characteristic, it may represent an applicability issue. The model does not permit changes to the TNBC:HR+ proportion in a way that varies the treatment effect of olaparib.
- 6.53 The model time horizon is 40 years. If olaparib results in avoided recurrences, then the IDFS curves will remain separated for the lifetime of a patient. At the end of the model lifetime, with a higher *BRCA* specific mortality rate applied, more than 40% of patients remain alive in both arms of the model. Therefore, the model time horizon is insufficient to capture the differences between the curves in the base case. If the goal of the model is to capture the differences in costs and outcomes associated with the use of olaparib, a shorter time horizon would not be reasonable. However, extrapolating costs and outcomes over a 40-year time horizon is associated with uncertainty which may be reduced over shorter time horizons. The ESC considered a time horizon of 30 years would be appropriate for consistency with other models in this setting.
- 6.54 The model structure is complex, and contains 5 health states. The submission has adopted a semi-Markov method (an approach that permits time varying transition probabilities) to calculate health state membership. The submission stated this was required because trial data were immature, and extrapolation of the trial survival curves was uncertain and therefore a partitioned survival analysis was not possible. However, five of the seven transition probabilities applied in the model were derived from the key trial. A more pragmatic approach may have been achievable and would likely have made some of the implicit assumptions more transparent.
- 6.55 The model functions to direct recurrences, initially derived from the IDFS curve of the OlympiA trial, to recurrence health states. The key assumptions driving the model results relate to the early modelled recurrence rates – particularly in the period immediately following the observed trial data.
- 6.56 Except for the transition from IDFS (TP3) and late-onset mBC to death (TP7), health state membership was largely informed by curves derived from the OlympiA trial. However, following 5 years, transitions from IDFS to recurrence health states are calculated from external data and applied equally across the curves. The submission assumed that the rates were equal across the model arms (applied the olaparib trial data to both arms), which was not justified. Using arm specific transition probabilities from early-onset mBC to death has been applied in the evaluation alternative base case (Table 17). Changing the year at which the olaparib arm is exposed to approximately 1% per year recurrence from year 5 to year 6 is explored in sensitivity analyses.

- 6.57 The submission uses a 2-year cut-off point to sort early-onset metastatic recurrences from late-onset metastatic recurrences. The submission notes that early-onset metastatic recurrences are likely to be those that are less amenable to subsequent therapies and are therefore at higher risk of death. This may be reasonable. However, the application of the same 2-year time point for the olaparib arm and the placebo arm of the model implies that recurrence within 2 years of the start of adjuvant therapy means the same thing as recurrence within 2 years of no treatment. During the OlympiA trial 105 patients in the olaparib arm and 169 patients in the placebo arm developed metastatic disease. Of these patients 70 in the olaparib arm and 103 in the placebo arm then died during the time frame of the study.
- 6.58 The submission presented the time from metastatic disease to death from the OlympiA trial (Figure 3). While the number of patients with metastatic disease was higher in the placebo arm, they were, on average, at a lower risk of death than those patients who were diagnosed with metastatic disease while receiving, or soon after receiving, olaparib. The model was moderately sensitive to the use of the same transition probability from early-onset mBC to death.

Figure 3: Kaplan-Meier data for time from metastatic disease to death in the OlympiA trial (by arm), DCO2



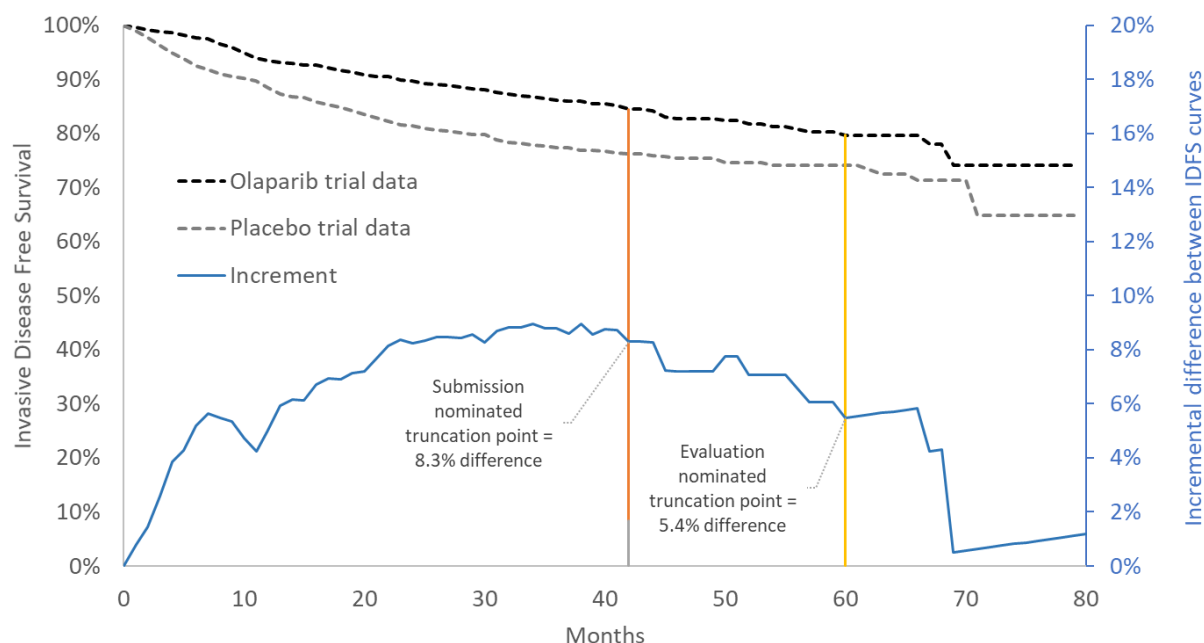
Source: Attachment 3.2 of the submission, Parametric reports from OlympiA, “Parametric-survival-analysis-OlympiA_DM_to_Death_ITT_population”.

DCO2 = data cut-off 2 in the OlympiA trial.

- 6.59 The submission nominated 42 months (median follow up in the OlympiA trial) as the data truncation point for using observed data. Following this time point, the submission used a parametric function until 5 years. This was not well justified. The difference in the IDFS Kaplan-Meier curves was substantially larger at this truncation

point than later data cut points (Figure 4). There were adequate numbers at risk in the OlympiA trial to extend the use of observed data to 5 years. The nominated parametric functions for this extrapolation do not accurately reflect the IDFS Kaplan-Meier curve for the placebo arm between 42 months and 60 months. The model results were highly sensitive to the nominated data truncation point as this largely generated the increment of long-term survivors modelled for the lifetime of the model.

Figure 4: Observed invasive disease-free survival curves and difference between the curves, with data truncation points



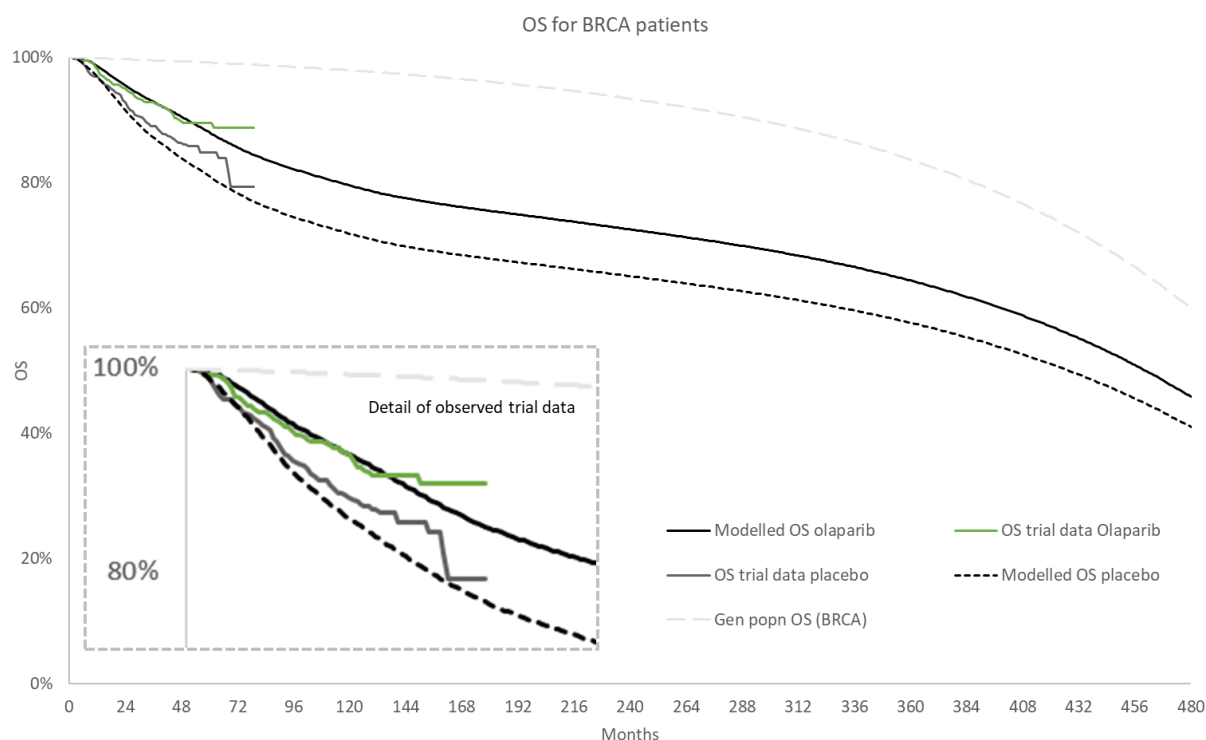
Source: generated during the submission from the economic evaluation spreadsheet.

Note, IDFS axis starts at 40%.

IDFS = invasive disease free survival.

6.60 The modelled OS curves were not based on the observed OS Kaplan-Meier curves from the OlympiA trial, but were a product of the transition probabilities in the model. While the survival curve appeared to reasonably fit the olaparib arm observed data, it was considerably below the placebo arm. The model appeared to overestimate the difference in survival across the arms compared with the observed KM data (Figure 5). Partly, this was due to the application of the same transition probability for the transition from early-onset metastatic breast cancer to death. However, correcting this only lifted the start of the placebo OS curve, and by about 8 years into the model, the 'corrected' OS curve merges with the modelled base-case OS curve (i.e. the same proportion of patients have died).

Figure 5: Modelled OS curves for *BRCA*-mutated patients (with background mortality in *BRCAm* patients)



Source: Adapted from Figure 3.29, p228 of the submission.
BRCAm = Pathogenic variant in the breast cancer gene; OS = overall survival.

- 6.61 The submission estimated utilities for the IDFS health state by mapping EORTC QLQ-C30 questionnaire results to the EQ-5D instrument using a mapping algorithm. This resulted in an estimate of 0.869 for the IDFS health state when estimated using a UK value set. The resulting utility estimate was higher than other published estimates, and possibly higher than the age-specific general population estimate of utility. The evaluation considered it was unlikely that patients would retain a general population utility estimate of a 43 year old for the full 40 years of the model.
- 6.62 Utilities were assumed to be the same across arms. No disutility is applied during treatment with olaparib. The evaluation considered this may not be reasonable given the higher rates of Grade 3 and 4 AEs in the olaparib arms, and some clear differences in EORTC QLQ-C30 results during the 12 months in which patients receive olaparib.
- 6.63 Utility estimates for the metastatic health states were derived from the OlympiAD study (olaparib vs chemotherapy in the metastatic setting). Pre-progression utilities were used for the early-onset metastatic disease health state and post-progression utilities were used for the late-onset metastatic disease health state, which may not be reasonable.
- 6.64 The model applied costs for *BRCA* testing, managing adverse events (in both the IDFS and subsequent health states), disease monitoring, treatments in non-mBC and mBC health states and for terminal care (upon transition to dead). The estimates of unit costs were mostly reasonable, and did not have a marked impact on the model. The

costs resulting in the largest increment between the arms related to the cost of olaparib, testing costs and subsequent anti-cancer treatment.

Table 14: Incremental costs (discounted) disaggregated across resource type (for the trial based comparison^a)

Resource item	Olaparib	Placebo	Incremental	% of incremental
Olaparib	\$█	\$0	\$█	107.3%
Subsequent anti-cancer treatment (local and metastatic recurrence) ^b	\$9,264	\$12,999	-\$3,735	-7.4%
Surgery /radiotherapy post recurrence	\$1,135	\$1,560	-\$425	-0.8%
Adverse events	\$978	\$805	\$173	0.3%
Disease monitoring	\$5,556	\$5,773	-\$217	-0.4%
Terminal care	\$7,120	\$8,854	-\$1,734	-3.4%
Testing costs ^c	\$10,191	\$7,938	\$2,253	4.5%
Total	\$█	\$37,929	\$█	100.0%

Source: generated during the evaluation from the 'ICER results' worksheet of the economic evaluation spreadsheet.

^aA trial-based comparison is generated by setting the prevalence of *BRCA* to 100% and testing proportion to 100%. This results in an estimate of the cost per patient treated with olaparib. The trial based comparison is modelled over 40 years, but excludes all non*BRCA* populations.

^bIncluding administration costs

^cAlthough the testing proportion is set to 100% (to prevent the model costing false negatives), the costs are based on the difference between the current rate (74%) and assumed rate (95%).

6.65 The evaluation proposed that following costs may need to be revised:

- The model had costed only the incremental difference in testing rates from the current rate (assumed to be 74%) to the forecast rate (assumed to be 95%). The rate of g*BRCA* testing was taken from IpSOS data, and was based on patients with TNBC only. Rates of g*BRCA* testing are likely to be lower in patients with HR+ disease. The submission stated that testing rates in patients with HR-positive, HER2-negative disease was about 10%.
- The model assumed 100% of patients entering the mBC health state will be treated. This was inconsistent with the rate of treatment observed in the OlympiA trial, which was about 70% of all patients with a recurrence event.
- Sacituzumab govitecan and palbociclib are subject to a special pricing arrangements.
- The model assumed 100% of the proposed dose for sacituzumab govitecan, however the relative dose intensity is likely between 70-80% (paragraph 7.18, 5.11 sacituzumab govitecan, public summary document [PSD], November 2021 PBAC meeting).

6.66 The evaluation stated that key drivers of the model were difficult to ascertain, as some of the possible drivers were structural (such as the time point at which the recurrence rate is reduced to approximately 1% per year, and the cut-off for early-onset vs late-onset mBC).

Table 15: Key drivers of the economic evaluation

Description	Method/Value	Impact Base case ICER \$ ¹ /QALY
Truncation point for observed data	The model used observed data up to 42 months for the IDFS curve (median follow up in the OlympiA trial, 41% of patients remain at risk). A parametric function was used to extrapolate the data to 60 months before adopting a common recurrence rate for both arms.	High, favours olaparib. There were adequate data available to extend the truncation point. At 60 months, the trial has 151 patients, or 14% of the trial population at risk. There was no indication in the KM curves at 5 years that small numbers were causing instability. The KM curves start converging from approximately 40 months onwards. Applying a data truncation point for the IDFS curve increases the ICER by 40% to \$ ² .
Current rate of gBRCA testing	The model assumed 74% of all patients with high-risk eBC will have been tested for germline BRCA mutations.	Moderate, favours olaparib. The rate of gBRCA testing in TNBC patients is reported to be 74%. This has rapidly increased over the 2 years of IpSOS data from 38% in 2020 to 74% in 2022. The cause of this rapid increase is unknown. Data for HR+ patients was not presented, however the submission noted that it was approximately 10%, but also that this included low risk patients. Assuming that 20% of HR+ patients receive testing, and 74% of TNBC patients receive testing increases the ICER by 8.6% to \$ ¹ .
Age in the model	Patients enter the model at age 43 years. This is the mean age in the OlympiA trial.	Moderate, favours olaparib. The mean age of gBRCA mutation positive, high-risk early breast cancer patients in the Australian setting may be higher (an Australian study of patients with TNBC who are gBRCA mutation positive reported the average age to be 50.3 years). Average age alters the influence of background mortality, which is the primary mechanism that reduces the incremental difference in the IDFS curves across the arms. The ESC considered an average age of 50 years was appropriate for the economic model consistent with the Australian study published by Wong et al (2015) ^a . Changing the average age in the model to 50 years of age increases the ICER by 6.35% to \$ ¹ .
Health state utilities	IDFS: 0.869 non-mBC: 0.7875 early-onset mBC: 0.706 late-onset mBC: 0.678 The utilities applied in the model are uncertain. They were derived using a mapping algorithm that converts EORTC QLQ-C30 results to EQ-5D results, which are then converted to utilities using UK value sets.	Moderate, favours olaparib. The utilities were high compared with some estimates in the literature. The utility value for IDFS is approximately the same as the age-specific general population estimate for a 43 year old. Applying literature based utility estimates for IDFS (0.805), non-mBC (0.708) and mBC (0.604) results in an increase in the ICER of 7.3% to \$ ¹ . The PSCR noted that use of published utility estimates in the commentary (Seferina 2017) come from a smaller population than OlympiA and may not be directly comparable to the proposed PBS population (non-BRCA HER2-positive). The ESC considered that utility values remain an area of uncertainty, however it proposed to revert to the health state utilities used in the submission's base case for the ESC respecified base case as the revised estimates were not considered to be more reliable than the trial based values.

Description	Method/Value	Impact Base case ICER \$ ¹ /QALY
Risk of death in the early-onset mBC health state	The risk of death was derived from the olaparib metastatic disease to death survival curve, and applied to both arms of the model.	Moderate, favours olaparib. The risk of death following diagnosis of metastatic disease was substantially higher in the olaparib arm. Applying the trial based hazard ratio to the placebo arm (HR = 0.668) resulted in an increase in the ICER of 5.14% to \$ ¹ .
Structural uncertainty relating to the 5-year reduction in recurrence risk assumption	Following 5 years of IDFS (informed by observed data to 42 months, then parametric functions to 5 years), the model applied the same risk of recurrence across the arms (approximately 1% per year).	High to very high, favours olaparib. The validity of this assumption was difficult to test. If olaparib both avoids and delays recurrence, it may not be reasonable to assume the same recurrence rate at 5 years for both arms. However, no alternative cut-off for the olaparib arm was available. Delaying the application of a 1% per year recurrence rate in the olaparib arm to 6 years, while retaining it at 5 years for the placebo arm increases the ICER by 17.2% to \$ ² .
Model time horizon	The average age entering the model was 43 years. At the end of the 40 year time horizon, a substantial proportion of both arms (>40%) remain alive.	Moderate, favours placebo. Data were not provided in the model to permit a longer time horizon to be used. However, only 10% of the discounted life years were accrued in the final 10 years of the model. As the proportion surviving beyond 40 years will likely reduce rapidly, and due to discounting, extending the model time horizon may not have a large impact on the ICER. A time horizon of 30 years increases the ICER by approximately 10% to \$ ¹ in the submission base case, and by approximately 7.7% in the commentary alternative base case from \$ ³ to \$ ³ .
Discount rate	5% for costs and outcomes.	High, favours placebo The goal of treatment with olaparib is to delay recurrence and to avoid recurrence. In those patients for whom recurrence is avoided, some may expect to live up to, or beyond, the model time horizon. However, the cost of olaparib is entirely undiscounted. Reducing the discount rate to 3.5% for both costs and outcomes reduces the ICER by 19% to \$ ⁴ .

Compiled during evaluation based on Section 3.9 of the submission and the economic evaluation spreadsheet.

^a 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.

eBC = early breast cancer; EORTC QLQ-C30 = European Organisation For Research and Treatment - Quality of Life Questionnaire for cancer patients; EQ-5D = EuroQol five dimension scale questionnaire ; g*BRCA* = germline breast cancer gene; HR+ = hormone receptor positive; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; IDFS = invasive disease free survival; KM = Kaplan-Meier; mBC = metastatic breast cancer recurrence; non-mBC = non-metastatic breast cancer recurrence; QALY = quality-adjusted life years; TNBC = triple-negative breast cancer.

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

³ \$95,000 to < \$115,000

⁴ \$35,000 to < \$45,000

6.67 The submission presented a stepped economic evaluation. The first step presented the results of an analysis at 79 months (the extent of the observed trial data). The analysis reported on invasive disease-free years, and the costs of olaparib, g*BRCA* testing, and the management of adverse events for olaparib or placebo. The second step presented the total model costs and life-years. The third step presented quality-adjusted life-years after application of utilities to the health states.

6.68 For additional information, the incremental cost per avoided recurrence was calculated during the evaluation (Step 1a), based on the increment reported at the extent of trial data (79 months).

Table 16: Results of the stepped economic evaluation

Data	Costs			Health outcomes			Incremental cost-effectiveness ratio
	Proposed medicine	Comparator	Incremental	Proposed medicine	Comparator	Incremental	
	Test costs, olaparib costs and adverse events costs			Invasive disease-free years			
Step 1: Trial based analysis	\$█	\$1,693	\$█	5.71	5.24	0.47	\$█ ¹ per disease-free year gained
				Recurrence at 79 months (per modelled data)			
Step 1a: Trial based analysis	As above			78.0%	69.7%	8.3%	\$█ ² per avoided recurrence
	As above plus cost of disease monitoring, subsequent therapies, and palliative care			Discounted life years			
Step 2: Modelled analysis (LYs)^a	\$█	\$37,929	\$█	14.32	13.15	1.169	\$█ ³ /LYG
	As above			Transformation using utility values for IDFS, non-mBC and mBC health states			
Step 3: Modelled analysis (QALYs)^a	\$█	\$37,929	\$█	12.360	11.321	1.039	\$█ ⁴ /QALY

Source: Generated during the evaluation from the economic evaluation spreadsheet.

^aModelled 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 12.6% of the cost of olaparib. The ICER remains the same as the benefits are also only 12.6% of the whole population. However, the numbers are not intuitive.

IDFS = invasive disease free survival; LY = life years; LYG = life years gained; mBC = metastatic breast cancer recurrence; non-mBC = non-metastatic breast cancer recurrence; QALY = quality-adjusted life years.

The redacted values correspond to the following ranges:

¹ \$115,000 to < \$135,000

² \$655,000 to < \$755,000

³ \$35,000 to < \$45,000

⁴ \$45,000 to < \$55,000

6.69 The commentary stated that key uncertainties in the model related to assumptions implicit in the structure of the model. Briefly, there was an assumption that, at 5 years following the initiation of adjuvant therapy (or placebo), the recurrence rate was reduced and was equivalent across the arms. By 10 years into the model, no recurrences were modelled. This resulted in two major concerns. Firstly, it assumed that the entire difference between the olaparib IDFS curve and the placebo IDFS curve at 5 years was a consequence of people being cured of eBC by olaparib, rather than being delayed. Secondly, by applying a lower rate of recurrence and then no recurrence, the opportunity for recurrences to narrow the distance between the olaparib IDFS curve and the placebo IDFS curve was limited. Increasing recurrence

rates during this time, even if set to equivalent across the arms, would affect the olaparib curve more due to the greater proportion of patients in the IDFS health state.

- 6.70 The application of a reduced recurrence at 5 years in both arms may not be justified. The application of a 1% (approx.) recurrence rate from 5 years to 10 years was based on published data in which adjuvant therapy was unlikely used, and no comparison of the rates between a population that received adjuvant therapy with a PARP inhibitor versus no treatment have been provided. It is possible that the use of olaparib could result in a recurrence occurring at for example, 6 years in a patient that would have otherwise recurred at 4 years. That recurrences could have been substantially delayed, rather than avoided altogether, might be evidenced by the reducing increment between the IDFS curves of the olaparib and placebo arms towards the end of the trial period.
- 6.71 There were no data to support the use of a 5 year cut-off beyond which recurrences are uninfluenced by olaparib, and there were no data to support the use of alternative cut-off points that may be different across the arms. However, the model is substantially sensitive to extending the cut-off in the olaparib arm to 6 years.
- 6.72 The commentary proposed an alternative base case as shown in Table 17.

Table 17: Stepwise multivariate sensitivity analyses to generate the evaluation alternative base case

Description of change	Base case value	Alternative value	ICER (cumulative)	Change in ICER
Base case			\$█ ¹	0%
Increase the average age	43 years	50 years	\$█ ¹	6.35%
Change the rate of gBRCA testing	74%	33.5% Weighted average of 74% for TNBC, 20% for HR+	\$█ ²	15.51%
Proportion of recurrences that are metastatic	Placebo: 76.8% mBC Olaparib: 75.4% mBC	76.2% mBC for both arms 23.8% non-mBC for both arms	\$█ ²	17.53%
Observed data truncation point	42 months	60 months	\$█ ³	64.97%
Risk of death from early-onset mBC	Olaparib survival curve	Arm specific	\$█ ³	78.04%
Rate of treatment in metastatic health state	100%	70%	\$█ ³	80.64%
RDI applied to sacituzumab govitecan treatment	100%	75%	\$█ ³	81.37%
Echo scans during follow up	Quarterly	Removed	\$█ ³	81.99%
Disutility applied to treatment with olaparib	0%	5% to the IDFS health state for 12 months	\$█ ³	94.62%
Health state utilities applied using real-world EQ-5D results for patients receiving adjuvant treatments	IDFS: 0.869 non-mBC: 0.7875 early-onset mBC: 0.706 late-onset mBC: 0.678	IDFS: 0.805 non-mBC: 0.708 mBC: 0.604	\$█ ⁴	106.90%
Evaluation alternative base case	All steps above	See above	\$█⁴	106.90%

Source: generated during the evaluation from the economic evaluation spreadsheet.

EQ-5D = EuroQol five dimension scale questionnaire ; gBRCA = germline breast cancer gene; ICER = incremental cost-effectiveness ratio; IDFS = invasive disease free survival; mBC = metastatic breast cancer recurrence; non-mBC = non-metastatic breast cancer recurrence; RDI = relative dose intensity.

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

⁴ \$95,000 to < \$115,000

- 6.73 The evaluation alternative base case resulted in a doubling of the ICER. The ESC noted the stepwise MSA presented in the commentary generated an ICER of \$95,000 to < \$115,000/QALY as shown in Table 17, however considered that additional alterations were required as described below.
- 6.74 The PSCR noted that use of published utility estimates in the commentary (Seferina 2017) come from a smaller population than OlympiA and may not be directly comparable to the proposed PBS population (non-BRCA HER2-positive). The ESC considered that utility values remain an area of uncertainty, however it proposed to revert to the health state utilities used in the submission's base case for the ESC respecified base case as the revised estimates were not considered to be more reliable than the trial based values.
- 6.75 The ESC advised that an additional step should be conducted in the ESC alternative base case in relation to the BRCA mortality ratio. The ESC considered the reliability of the model would be improved if the standardised mortality ratio (SMR) was adjusted as proposed in the commentary. The SMR in the submission was derived from a study that removed all cancer deaths. Patients with gBRCA mutations have a substantially

higher rate of ovarian (and other cancers), and may experience an increased mortality due to new cancers. The submission base case used a standardised mortality ratio (SMR) of 1.46 which was assumed to be constant over time. The commentary considered that a more likely SMR, to capture death from non-breast cancer malignancies, should be higher than that which has been proposed, and proposed a sensitivity analysis applying an SMR=2.

6.76 The ESC advised that the following changes should be made to the economic model as compared with the evaluation alternative base case, while noting that uncertainties remained with respect to assumptions implicit in the structure of the model (paragraph 6.69). The ESC noted the ESC alternative base case generated an ICER of \$95,000 to < \$115,000/QALY as shown in Table 18.

- Revert to health state utilities used in the submission's base case (see paragraph 6.73)
- Time horizon of 30 years consistent with other models in this setting (paragraph 6.52)
- Increasing the background mortality for gBRCAm patients to account for other cancer deaths (paragraph 6.75)

6.77 The Pre-PBAC response stated that gBRCAm patients are significantly younger at diagnosis than sporadic breast cancer patients and stated that the population reported in the Wong-Brown 2015 study may have more advanced disease than the proposed PBS population. The PBAC considered that the average age of patients diagnosed with breast cancer is substantially lower if they harbour gBRCA mutations than if they do not have gBRCA mutations, and noted that a starting age of 43 years would reflect the mean age in the OlympiA trial. The Pre-PBAC response stated that the maximum disutility applied to olaparib should be 0.6% as per trial-based utility scores presented in the submission. The PBAC considered it would be appropriate to apply a starting age of 43 in the economic model, a disutility of 0.6% applied to treatment with olaparib, and apply all other inputs as advised by the ESC, which generated an ICER of \$75,000 to < \$95,000/QALY (Table 18).

Table 18: Stepwise multivariate sensitivity analyses to generate the ESC respecified base case and PBAC analysis

Step	Variable or assumption	ICER (\$)	Percent change from base case
	Submission Base case	1	0.0%
	ESC RESPECIFIED BASE CASE		
1	Increase the age in the model to 50	1	6.35%
2	Apply a lower rate of current testing for HR+ patients (33.5% weighted average)	2	15.51%
3	Type of recurrence equal across the arms in the model	2	17.53%
4	60 month truncation point for the use of observed data	3	64.97%
5	Risk of death from early-onset mBC different across arms	3	78.04%
6	Reduced rate of treatment in the mBC health state	3	80.64%
7	Relative dose intensity applied to sacituzumab govitecan (TNBC, mBC)	3	81.37%
8	Cost of echocardiography removed from monitoring costs	3	81.99%
9	Disutility applied to treatment with olaparib (5%) ^a	3	94.62%
10	Time horizon set to 30 years	4	109.80%
11	Increase background mortality for gBRCAm patients to account for other cancer deaths	4	115.99%
	PBAC RESPECIFIED BASE CASE		
1	Reset age to 43 years	4	105.65%
2	Adjust disutility applied to treatment with olaparib (0.6%) ^b	3	93.14%

a. Applies 5% disutility to the olaparib arm in the IDFS health state for 12 months, compared with 0%.

b. Applies 0.6% disutility to the olaparib arm (as described in pre-PBAC response) in the IDFS health state for 12 months. Shading indicates consistent with the Evaluation alternative base case (Table 17).

Source: Generated from the economic evaluation spreadsheet.

EQ-5D = EuroQol five dimension scale questionnaire ; gBRCA = germline breast cancer gene; HR+ = hormone receptor positive; ICER = incremental cost-effectiveness ratio; mBC = metastatic breast cancer recurrence; TNBC = triple-negative breast cancer.

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

⁴ \$95,000 to < \$115,000

Olaparib cost/patient/course**Table 19: Drug cost per patient for olaparib**

	Trial dose and duration	Model	Financial estimates
Mean dose	565 mg/day ^a	600 mg ^b	600 mg ^b
Mean duration	9.7 months	10.267 months ^c	11.5 months ^d
Cost/patient/month ^a	NA	\$ ⁱ	\$ ^e
Revised			\$ ^f
Cost/patient/course	NA	\$ ⁱ	\$ ^g
Revised			\$ ^h

Source: Table 14.3.1.1, Attachment 2.4 to the submission, Section 3 workbook, sheet 'Markov – P1 (BRCA)', Section 4 workbook.

^a Based on effective DPMQ

^b The mean daily dose of olaparib in the economic model is 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 150 mg tablets.

^c The mean duration of treatment derived from OlympiA time on treatment curve, adjusted down by 12 days to account for treatment interruptions.

^d Duration of treatment adjusted for compliance (96.15%)

^e This is based on submission's estimate for net olaparib cost to the PBS/RPBS (\$30 million to < \$40 million in Year 1), for a total of 500 to < 5,000 patients estimated in Year 1 for the 12 months of maximum treatment duration at a compliance of 96.15%.

^f This is based on revised estimate for net olaparib cost to the PBS/RPBS (\$60 million to < \$70 million in Year 1) for a total of 500 to < 5,000 patients estimated in Year 1 for the 12 months of maximum treatment duration at a compliance of 96.15%.

^g This is calculated by multiplying the submission's estimate for net olaparib cost to the PBS/RPBS (\$30 million to < \$40 million in Year 1) by the estimated total number of patients (500 to < 5,000 in Year 1).

^h This is calculated by multiplying the revised estimate for net olaparib cost to the PBS/RPBS (\$60 million to < \$70 million in Year 1) by the estimated total number of patients (500 to < 5,000 in Year 1).

Estimated PBS usage & financial implications

6.78 This submission was considered by DUSC.

6.79 The submission used an epidemiological approach to estimate utilisation and financial implications of the proposed co-dependent technologies: olaparib + germline *BRCA* mutation test to identify *BRCA1* or *BRCA2* mutations in patients with HER2-negative, high-risk, early breast cancer. To estimate the number of germline *BRCA*-mutated HER2-negative high-risk eBC patients eligible for adjuvant olaparib treatment, the financial analysis encapsulated two subgroups: TNBC, and HR-positive, HER2-negative BC. The DUSC noted that the submission estimates contained an error which underestimated the number of scripts per patient, and that the sponsor provided revised estimates with the PSCR (see paragraph 6.82).

6.80 The key inputs in the financial analysis are summarised in Table 20.

Table 20: Key inputs for financial estimates

Parameter	Value applied and (source)	Comment	PBAC advice for amendment
Incident cases of breast cancer	21,233 in Year 1 of listing, increasing to 23,678 in Year 6 (AIHW Cancer in Australia 2021 report)	DUSC agreed with the commentary that the incidence projections were appropriately sourced.	

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Parameter	Value applied and (source)	Comment	PBAC advice for amendment
Incidence of early (Stage I-III) breast cancer	89.81% (AIHW Australian Cancer Database 2014 Table S3.1)	This data for staging distribution based on patients diagnosed in 2011 was not adjusted for patients of unknown disease stage (5.5%). DUSC agreed with the commentary and considered the sponsor's approach in the PSCR to be more appropriate.	The PBAC agreed with DUSC that the estimate should be adjusted to 95.08% as in the commentary and PSCR.
Proportion of patients with TNBC	12.10% (Stuart-Harris et.al. 2019)	Lower than the estimate (15%) previously used for PBAC decision making for atezolizumab submissions in March 2020, and March 2021 resubmission. DUSC agreed with the commentary in that 12.10% is likely an underestimate.	PBAC considered an estimate of 15% would be appropriate, consistent with previous considerations which had assumed 15% based on an estimate sourced from Cancer Council Australia (Table 16, atezolizumab PSD, March 2021 PBAC meeting).
Proportion of high-risk TNBC patients	The submission did not estimate the proportion of TNBC patients that would be considered high risk, which is an eligibility requirement for the proposed PBS listing.	Pathological complete response (pCR) may occur after chemotherapy and that patients with pCR are not eligible for olaparib under the proposed listing.	The PBAC considered that an estimate of 40% high-risk (eligible) should be used, on the basis of trial data in the neoadjuvant setting indicating a pCR rate between 50 and 65%. (Schmid et al 2020 ²¹)
Proportion of HR-positive, HER2-negative breast cancer	69.3% = 81.8% x 84.7% (The combined probability was calculated by multiplying the proportions of patients with HR-positive breast cancer and patients with HER2-negative breast cancer reported in study by Stuart-Harris et.al. 2019)	The source and calculation were reasonable. DUSC considered this to be appropriate.	The PBAC considered the estimate of 69.3% was reasonable (unchanged from submission estimates).
Proportion of high-risk HR-positive, and HER2-negative breast cancer patients	49.0% (The sum of proportion of patients using neoadjuvant (4.43%) and adjuvant chemotherapy (44.57%) reported in Patiniott et.al. 2019).	The approach of using proportions of patients on (neo)adjuvant chemotherapies as a proxy to estimate patients at high risk was reasonable. DUSC considered this to be appropriate.	The PBAC considered this was overestimated, and a rate of 25% would be more appropriate for the HR+ population.

²¹ Schmid P et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821.

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Parameter	Value applied and (source)	Comment	PBAC advice for amendment
Germline <i>BRCA</i> mutation testing uptake rates	<p><u>Current test rates in TNBC patients (in Q1 2022)</u> 74% (Stage I-IIIa), 64% (Stage IIIb-IV), 67% (overall) (<u>IPSOS report commissioned by sponsor</u>)</p> <p>Current test rates in HR+ patients, assumed to be 74% (sponsor assumption, equal to TNBC)</p>	<p>Current rate (74%) is uncertain and likely overestimated as the eBC incident patients include Stage I-III, not only Stages I-IIIa.</p> <p>Uptake rates are uncertain, no data is available to support this assumption in patients with HR-positive, and HER2-negative high-risk breast cancer.</p> <p>DUSC agreed with the commentary and noted that this input may be biased as it was taken from a TNBC population where testing would be higher compared to hormone receptor positive patients.</p>	<p>The PBAC considered that 74% would be appropriate for the TNBC population but that a lower estimate of 20% should be assumed for the HR+ population consistent with the advice regarding the economic model (see Table 17).</p>
	<p><u>Uptake rate for germline <i>BRCA</i> mutation tests:</u> Ranging from 80% in Year 1 increasing to 95% in Year 6. Based on assumption.</p>	<p>DUSC considered this to be appropriate however noted it may be higher in initial years.</p>	<p>The PBAC considered that testing in the TNBC population would remain higher than the HR+ population, and proposed that 74% uptake should be assumed for TNBC and 20% for HR+ population in Year 1 consistent with the row above (and the assumptions in the economic model).</p> <p>The PBAC considered that the uptake rate for germline <i>BRCA</i> testing would increase to 85% from Year 2 for TNBC, and to 30% from Year 2 for HR+.</p>
Germline <i>BRCA</i> prevalence rate	<p>13.25% = (9.34%+15%+15.4%)/3 Simple mean of Australian evidence from IPSOS report (15%), Wong-Brown et al 2015 (9.34%), Armstrong et.al. 2019 (9.3%-15.4%).</p>	<p>IPSOS data (15%) could not be located, and uncertain. The US data for germline <i>BRCA</i> mutation (15.4%) is not representative of Australian population.</p>	<p>The PBAC considered that the results would differ for TNBC and HR+ populations, and considered that the following assumptions for the percentage <i>BRCA</i>+ should be used: 13.25% for TNBC and 5% for HR+ (Southey et al 2021²²).</p>
Adverse event (AE) management or Disease monitoring costs	Not estimated	<p>This was inconsistent with the economic analysis. DUSC agreed with the commentary and considered that AE related costs should have been included in the estimates.</p>	

²² Southey MC, et al. Population-based estimates of breast cancer risk for carriers of pathogenic variants identified by gene-panel testing. NPJ Breast Cancer. 2021 Dec 9;7(1):153.

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Parameter	Value applied and (source)	Comment	PBAC advice for amendment
Olaparib treatment uptake rate	Ranging from 95.0% in Year 1 to 99.0% (Year 6), based on assumption.	This was reasonable, as it referred to uptake within a population that underwent <i>BRCA</i> mutation testing, and tested positive.	
Grandfathered patients	█████ ¹ patients, estimate of patients in Patient Access Program by sponsor	This is uncertain and likely an overestimate. DUSC considered this to be uncertain but unlikely to impact cost and utilisation dramatically.	
Average duration of treatment per patient	12 months (OlympiA CSR)	The submission claimed to have costed maximum treatment duration of 12 months, but only effectively costed 6 months of treatment. Further, it may be more reasonable to apply the mean treatment duration in the trial (9.7 months (= 295.0 days x 12 months / 365.25 days). DUSC agreed with the commentary that it would be more reasonable to apply the mean treatment duration from the trial to the estimates as this would also implicitly account for compliance.	The PBAC considered that the estimates should apply the mean treatment duration from the trial, 9.7 months.
Compliance	96.15% The median actual treatment exposure (350 days) vs median total intended (364 days) in OlympiA CSR (DCO2: 12 days per patient, in which the daily dose is 0mg).	As above, it would be more appropriate to use the mean duration of treatment per patient 9.7 months from the trial, which has taken compliance into account.	
Scripts dispensed	█████ ² in Year 1 increasing to █████ ² in Year 6. Based on average of 12.54 packs per patient, and a compliance of 96.15%.	The submission claimed to apply 12.54 packs per patient. However, the total number of scripts per patient were divided by two in the submission, which the PSCR confirmed was due to an error. DUSC acknowledged the PSCR which provided updated and corrected estimates.	

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Parameter	Value applied and (source)	Comment	PBAC advice for amendment
Germline <i>BRCA</i> mutation testing	\$1,200 (Schedule fee), Benefit at 80% = \$960 Based on MBS item 73296	Similar to the number of scripts, the total number of germline <i>BRCA</i> mutation testing services appear to be erroneously divided by two in the submission. As majority of the patients might receive germline <i>BRCA</i> mutation test at out-of-hospital setting, benefits at 85% rebate rate might be more reasonable. The Greatest Permissible Gap (GPG) ^a amount was not considered in the submission. DUSC agreed with the commentary that these costs were underestimated.	
Germline <i>BRCA</i> mutation cascade testing	Not estimated	MBS costs likely underestimated	
Genetic counselling	Not estimated	MBS costs likely underestimated	

Source: Compiled during the evaluation from information provided in Section 4 of the submission and the Excel workbook 'Att_4.1_OlympiA UCM_FINAL'.

AIHW = Australian Institute of Health and Welfare; *BRCA* = Breast Cancer gene; CSR = clinical study report; eBC = early breast cancer; GPG = Greatest Permissible Gap; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; MBS = Medicare Benefits Schedule; PSD = public summary document; TNBC = triple-negative breast cancer

^a From 1 November 2022, the GPG and the GPG threshold values are set at \$93.20, \$621.50, respectively.

The redacted values correspond to the following ranges:

¹ < 500

² 5000 to < 10,000

- 6.81 The estimated use and financial implications for the PBS listing of olaparib and the codependent MBS listing of the germline *BRCA* mutation test are summarised in Table 21.
- 6.82 The PSCR presented revised financial estimates as shown below. DUSC noted that the revised estimates corrected the number of prescriptions but the assumption of 12 months of treatment duration, adjusted for compliance based on the average relation dose intensity of 96.15% was retained, which appeared overestimated in comparison to the average treatment duration in OlympiA of 9.7 months. The PSCR stated that target PBS population will be younger and patients were expected to complete their treatment.

Table 21: Estimated use and financial implications (based on proposed effective price for olaparib)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Incidence early breast cancer	█ ¹	█ ¹	█ ¹	█ ²	█ ²	█ ²
Estimated extent of use BRCA1/2 pathogenic gene variant test						
A gBRCA mutation tests in TNBC patients (olaparib available), Proposed uptake Years 1-6: 80-95%	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
B gBRCA mutation tests in TNBC patients (olaparib not available), Current uptake Years 1-6: 74%	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
C Incremental gBRCA mutation tests in TNBC patients (C = A – B)	█ ⁴	█ ⁴	█ ⁴	█ ³	█ ³	█ ³
D gBRCA mutation tests in HR(+)/HER2(-) high-risk eBC patients (olaparib available), Proposed uptake Years 1-6: 80-95%	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
E gBRCA mutation tests in HR(+)/HER2(-) high-risk eBC patients (olaparib not available), Current Uptake Years 1-6: 74%	█ ³	█ ³	█ ⁵	█ ⁵	█ ⁵	█ ⁵
F Incremental gBRCA mutation tests in High-risk HR+/HER2- patients (F = D – E)	█ ⁴	█ ³	█ ³	█ ³	█ ³	█ ³
G Total number of patients tested (proposed) (olaparib available) (G = A + D)	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
H Total no. patients tested (current) (olaparib not available) (H = B + E)	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
I Submission's estimate of change in testing [I = (G – H)/2] ^a	█ ⁴	█ ⁴	█ ³	█ ³	█ ³	█ ³
J Revised estimates of change in testing (J = G – H)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Estimated financial implications of the BRCA1/2 pathogenic gene variant test to the MBS						
K Submission's Net Cost to MBS (\$) (K = I x \$960.00 per patient)	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
L Revised ^b (\$) (L = J x \$1,106.80 per patient)	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Estimated extent of use of olaparib						
M Triple negative early breast cancer	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
N HR-positive, HER2-negative high-risk breast cancer	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
O Grandfathered patients	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
P Total number of patients (P = M + N + O)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
R Number of scripts dispensed (R = P x 6.27 per patient) ^c	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
S Revised ^d (S = P x 12.54 per patient)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated financial implications of olaparib to the PBS/RPBS						
T Net cost to PBS/RPBS (\$) (T = R x \$█ per script, excluding copayments)	█ ⁷	█ ⁸	█ ⁷	█ ⁷	█ ⁷	█ ⁷
U Revised (\$) (U = S x \$█ per script, excluding copayments)	█ ⁹	█ ¹⁰	█ ⁹	█ ¹¹	█ ¹¹	█ ¹¹

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	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
V	Net cost to Government Health Budget (PBS/RPBS/MBS) (\$)	■ ⁷	■ ⁷	■ ⁷	■ ⁷	■ ⁷
Y	Revised (Y = L + U) (\$)	■ ⁹	■ ⁹	■ ⁹	■ ¹¹	■ ¹¹
Revised estimate in PSCR - Estimated financial impact for the PBS/RPBS (effective price)						
	Net cost PBS / RPBS (\$)	■ ⁹	■ ⁹	■ ¹¹	■ ¹¹	■ ¹²

Source: Compiled during evaluation from information provided in Section 4 of the submission and the Excel workbook 'Att_4.1_OlympiA UCM_FINAL'.

gBRCA = germline breast cancer gene; GPG = Greatest Permissible Gap; HR(+) = hormone receptor positive; HER2 (-) = human epidermal growth factor receptor 2 negative; TNBC = triple-negative breast cancer;

^a The submission's estimated volume changes to the MBS item was calculated using '7. Net changes – MBS' spreadsheet in Excel workbook 'Att_4.1_OlympiA UCM_FINAL' by subtracting the sum of cells (M509:M510 through R509:R510) from the sum of (M113:M114 through R113:R114).

^b This is calculated by multiplying the change in use of germline BRCA testing services (i.e. 527 in Year 1, rather than 263 in Year 1 which was erroneously calculated in the '7. Net changes – MBS' spreadsheet) by the MBS fee (\$1,106.80) at 85% rebate rate accounting for the GPG, compared to \$960 at 80% rebate rate in the submission.

^c The number of scripts per patient per year applied in the submission was calculated by dividing the total olaparib prescription numbers presented in Table 4.11, p248 of the submission and '3a. Scripts – proposed' by the total number of patients.

^d This is calculated by multiplying the total number of patients by 12.54 scripts per patient per year (= 365.25 / 28 days for the number of scripts per year [13.04] multiplied by compliance, 96.15%).

the redacted values correspond to the following ranges:

¹ 10,000 to < 20,000

² 20,000 to < 30,000

³ 500 to < 5,000

⁴ < 500

⁵ 5,000 to < 10,000

⁶ \$0 to < \$10 million

⁷ \$30 million to < \$40 million

⁸ \$20 million to < \$30 million

⁹ \$60 million to < \$70 million

¹⁰ \$50 million to < \$60 million

¹¹ \$70 million to < \$80 million

¹² \$80 million to < \$90 million

6.83 The submission estimated the total cost to the PBS/RPBS of listing olaparib to be \$30 million to < \$40 million in Year 6, and a total of \$200 million to < \$300 million in the first 6 years of listing, which was revised during evaluation to be \$70 million to < \$80 million in Year 6 and \$400 million to < \$500 million over the first 6 years of listing based on the proposed effective price. The revised estimates in the PSCR totalled \$400 million to < \$500 million over the first 6 years of listing based on the proposed effective price.

6.84 The net cost to the MBS of listing germline BRCA mutation was estimated to be \$0 to < \$10 million in Year 6 (revised during evaluation to \$0 to < \$10 million), and a total of \$0 to < \$10 million over the first 6 years of listing (revised to \$10 million to < \$20 million). The total net cost to the government health budget was estimated to be \$30 million to < \$40 million in Year 6 (revised \$70 million to < \$80 million), and \$200 million to < \$300 million over the first 6 years of listing (revised as \$400 million to < \$500 million). The submission's approach to estimating the impact of listing germline BRCA testing was to cost only the increase in tests from current testing rates. This did not capture the likely shift from provision of services in state and territory health budgets to the MBS and therefore underestimated the financial impact to the MBS.

- 6.85 The submission claimed to have costed the 12 months maximum duration of treatment, but only effectively costed 6 months of treatment because the number of olaparib prescriptions and germline *BRCA* mutation testing services were erroneously divided by two. During evaluation the number of olaparib scripts was corrected as 10,000 to < 20,000 scripts in Year 1 increasing up to 10,000 to < 20,000 in Year 6 (compared to the submission's estimated olaparib scripts of 5,000 to < 10,000 in Year 1 increasing up to 5,000 to < 10,000 scripts in Year 6).
- 6.86 The evaluation identified uncertainties associated with epidemiological inputs and uptake assumptions for both drug population and test population estimates as follows:
- The eBC distribution rates for Stage I-III (89.81%) was an underestimate as it was not adjusted for patients of unknown disease stage (5.54%)
 - The proportion applied for the incident TNBC patients (12.1%) was lower than the estimate of 15% which was previously accepted by the PBAC for the atezolizumab submissions (paragraph 6.71, sacituzumab govitecan PSD, November 2021 PBAC meeting);
 - The uptake of germline *BRCA* testing (which defines the population eligible for olaparib treatment) is uncertain. The submission's assumption was based on use in a small sample of TNBC patients, with limited applicability to patients with HR-positive, HER2-negative high-risk breast cancer. No evidence was identified to support uptake assumptions in the HR-positive subpopulation.
- 6.87 The total cost to the MBS was revised during the evaluation, to correct an error in the estimated use of testing which the submission erroneously halved. When this error was corrected, the estimated number of germline *BRCA* mutation testing services increased to 500 to < 5,000 services in Year 1 compared to < 500 services as estimated by the submission.
- 6.88 In contrast to the economic analysis, the submission's estimates for the costs to the MBS did not include pre-/post-counselling fees, health care resource utilisations for drug monitoring or AE management associated with olaparib treatment. In addition, the submission applied an 80% MBS rebate (\$960.00). However, as the majority of patients are expected to receive germline *BRCA* mutation testing in the out-of-hospital setting, it may be more reasonable to apply an 85% rebate rate of \$1,106.80 accounting for the GPG.
- 6.89 The submission stated that < 500 patients were assumed to access olaparib via the sponsor's patient access program and all patients were assumed to transition to the PBS. Each grandfathered patient was assumed to receive a full course of olaparib treatment, which is likely to be an overestimate.

Quality Use of Medicines

- 6.90 The submission 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.
- 6.91 The intended supply arrangement (one initial and one continuing script, each with 5 repeats for a 28 days supply allows for a maximum of 336 days of therapy, and assumes zero loss of any single tablet. The requested restriction should facilitate full patient compliance with intended maximum duration of treatment (12 months) to avoid poor quality use of medicines, and any ethical and effectiveness concerns that may incur.

Financial Management – Risk Sharing Arrangements

- 6.92 The sponsor noted that there is a Deed of Agreement between The Commonwealth of Australia and AstraZeneca Pty Ltd in relation to sharing the costs of Commonwealth subsidy for the supply of olaparib (executed on [redacted] and updated [redacted] to include the SOLO1 listing). The submission stated that the sponsor is willing to work with the PBAC and Department of Health to determine appropriate terms for PBS listing of olaparib for eligible patients with HER2-negative high-risk early breast cancer.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend olaparib for the adjuvant treatment of human epidermal growth factor 2 negative (HER2-) high-risk early breast cancer with a confirmed germline *BRCA1* or *BRCA2* 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 IDFS was reported from the pivotal registration study, but that the OS data remained immature. Olaparib was inferior to placebo in terms of safety. The PBAC considered that the incremental cost-effectiveness ratio was highly uncertain and unacceptably high. The PBAC considered that revisions were also required to the financial estimates.
- 7.2 The PBAC considered that the proposed clinical place for olaparib was appropriate and noted that implementation of the listing would be reliant on access to *BRCA* testing as requested by the streamlined codependent submission.
- 7.3 The PBAC noted the input from individuals, and organisations and acknowledged that the Medical Oncology Group of Australia (MOGA) had 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.
- 7.4 The PBAC considered that the nomination of placebo ('watch and wait') as the main

comparator was appropriate. The PBAC considered that most hormone receptor positive 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 (see paragraph 3.3).

- 7.5 The PBAC noted that the primary clinical evidence supporting the clinical claim was a randomised, double-blind, multicentre phase 3 study (OlympiA) of olaparib (n=921) compared to placebo (n=915) as adjuvant treatment in patients with germline *BRCA1/2* mutations and high-risk HER2-negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. The PBAC noted that the OlympiA trial initially included TNBC patients only and that approximately 18 months after the trial had begun, an amendment to the protocol was made to include HR+, HER2- eBC patients. The OlympiA trial included a smaller proportion of HR-positive, HER2-negative patients (17.7%) compared with TNBC patients (82.3%).
- 7.6 The PBAC noted that key efficacy outcomes were statistically significantly improved in the olaparib group compared to the placebo group in the OlympiA trial at DCO2 (median follow-up of 3.5 years), including IDFS (HR = 0.63; 95% CI 0.50, 0.78), DDFS (HR = 0.61; 95% CI 0.48, 0.77), and OS (HR = 0.68; 98.5% CI 0.47, 0.97). 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 with only 8.1% of events occurring in the olaparib arm and 11.9% of events occurring in the placebo arm, at a median follow-up of 3.5 years. 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-positive group.
- 7.7 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 (Table 10). The PBAC also noted that MDS/AML was a concern with PARPis. The PBAC considered that olaparib had inferior safety in comparison with placebo.
- 7.8 The PBAC noted that the submission presented a cost-utility analysis, based on the ITT population from OlympiA. The economic evaluation compared the proposed scenario (in which germline *BRCA* testing is available and *BRCAm* patients are eligible for olaparib) with the comparator scenario (in which some germline *BRCA* testing occurs as per current clinical practice and treatment with placebo). The PBAC considered that the absolute size of the modelled benefit beyond the time horizon of the trial was subject to significant uncertainty and this translated to a highly uncertain ICER.
- 7.9 The PBAC considered that the base case ICER proposed by the submission was underestimated, and noted that several revisions had been proposed by the ESC for consideration (Table 18). The nominated time point for ceasing the use of observed KM data had a substantial impact on the ICER. The PBAC noted that the truncation

point in the submission's base case (42 months), was stated to reflect the median follow-up, however considered this resulted in the exclusion of a substantial amount of trial data as at this time point 41% of patients remained at risk. Further, review of the observed IDFS curves and difference between the curves (Figure 4) revealed a larger increment at 42 months as compared with 60 months and hence the use of 42 months potentially resulted in the extrapolated benefits being overestimated. The PBAC noted that use of the 42 month truncation point substantially increased the estimated LYs gained and uncertainty.

- 7.10 The PBAC noted the ESC base case scenario (see paragraph 6.77) revised the starting age of the modelled cohort from 43 years to 50 years on the basis of an Australian study published by Wong et al (2015), however the PBAC considered that the clinical trial population was a more reliable source for the model starting age on the basis that the average age of patients diagnosed with breast cancer is substantially lower if they harbour *gBRCA* mutations. The PBAC noted that application of a starting age of 43 years, a disutility of 0.6% applied to treatment with olaparib, and all other inputs as proposed by the ESC generated an ICER of \$75,000 to < \$95,000/QALY compared with the submission base case of \$45,000 to < \$55,000/QALY.
- 7.11 The PBAC noted that each of the additional revisions specified in Table 18 were associated with relatively minor changes to the ICER, however agreed with the ESC that the revised parameters were likely more appropriate. The PBAC also noted additional uncertainties arising from the model structure as discussed in paragraph 6.69.
- 7.12 The PBAC considered that olaparib could be considered cost-effective if the changes to the economic model were made as described in paragraph 7.10 and the ICER was approximately \$35,000/QALY, to account for the uncertainty in modelled benefit beyond the time horizon of the trial (see paragraph 7.8). The PBAC noted that a significant price reduction would be necessary to meet this ICER.
- 7.13 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 (Table 6). Accordingly, the hazard ratios for key outcomes were improved in the TNBC subgroup compared with the ITT population (IDFS HR: 0.62 compared with 0.63; and OS HR: 0.64 compared with 0.68). The PBAC noted it was not possible to estimate the ICER for these subgroups with the economic model provided in the submission because it did not contain the required KM data by subgroup (see paragraph 6.52). The PBAC expressed a preference for the proposed listing to reflect the ITT population of OlympiA, rather than limiting to the TNBC group, however 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. The PBAC considered that the results for the TNBC subgroup are more certain than for the HR+ subgroup given the larger number of TNBC patients included in the trial (82.3% of the ITT population), and the longer duration of follow-up in this subgroup given the protocol amendment which allowed HR+ patients into the trial occurred approximately 18 months after the first

patient was recruited to the study. The PBAC also considered that on average, recurrences are likely to occur later in the HR+ subgroup, compared with the TNBC subgroup (see paragraph 4.1, and 6.14), which further increases the uncertainty of long term outcomes for the HR+ subgroup. Although there is currently no statistical evidence of treatment-effect modification on the HR-scale, it is possible that with more mature data an underlying pattern of treatment-effect modification might be revealed. This lack of statistical power to detect treatment-effect modification added to the uncertainty in the ICER for the ITT population.

7.14 With regard to utilisation estimates, the PBAC considered that the patient numbers estimated by the submission were implausibly high. The PBAC considered that the estimates 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. The PBAC also considered that duration of treatment should be revised to reflect the utilisation in the OlympiA trial:

- Incidence of early (Stage I-III) breast cancer: adjust to 95.08%.
- Proportion of patients with TNBC: adjust to 15%.
- Proportion of high-risk TNBC patients: specify 40% (100% was assumed in submission).
- Proportion of high-risk HR-positive, and HER2-negative breast cancer patients: adjust to 25%
- Germline *BRCA* mutation testing uptake rates – Current test rates applied to Year 1: 74% for the TNBC population and 20% for the HR+ population.
- Germline *BRCA* mutation testing uptake rates – Future test rates if olaparib PBS listed (applied from Year 2 onwards): 85% for the TNBC population and 30% for the HR+ population.
- Germline *BRCA* prevalence rate: 13.25% for TNBC and 5% for HR+.
- Average duration of treatment per patient: apply the mean treatment duration from the trial, 9.7 months.

7.15 The PBAC noted that MSAC advice was also required in relation to the financial estimates in relation to MBS costs.

7.16 The PBAC considered the outstanding issues could be resolved in a simple resubmission for olaparib using the early re-entry pathway with a material price reduction to accommodate more plausible inputs into the economic model and allow for the uncertainty associated with the immature OS data. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

- Revise the economic model as per Table 18. The PBAC noted that the early re-entry pathway would not be appropriate if the model structure is revised.
 - Revise the base case as discussed in paragraph 7.10; and
 - A price reduction to result in an ICER of approximately \$35,000/QALY gained (paragraph 7.12).
 - Recalculation of the financial implications using revised inputs as discussed in paragraph 7.14 and revised olaparib price.
- 7.17 The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.
- 7.18 The PBAC noted that patients with de novo metastatic disease (roughly 5% to 15% of BRCA-positive patients in Australia) would not be able to access olaparib under the proposed listing (see paragraph 2.7). The PBAC noted that cost-effectiveness has not been assessed in this population and that the sponsor would need to lodge a PBAC submission to request listing of olaparib in the metastatic breast cancer setting to support appropriate consideration of this request. The PBAC noted that the implications to the MBS would need to be considered (see paragraph 2.10) and that the sponsor should seek advice from the Department if intending to lodge a submission.
- 7.19 The PBAC noted several concerns with the proposed restrictions as described in paragraph 3.12.
- 7.20 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.