6.03 OLAPARIB, Tablet 100 mg, Tablet 150 mg, Lynparza®, ASTRAZENECA PTY LTD

1 Purpose of submission

1.1 The Category 2 streamlined codependent PBAC/MSAC submission requested a General Schedule Authority Required (Telephone/Online) listing of olaparib for the treatment of human epidermal growth factor 2 negative (HER2-negative) metastatic breast cancer for patients with a confirmed *BRCA1* or *BRCA2* mutation. The proposed medical service would provide germline *BRCAm* testing to detect *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants in patients with HER2-negative metastatic breast cancer to determine eligibility for olaparib treatment.

1.2 The submission requested modification of the existing MBS item which currently applies for certain patients with ovarian, fallopian tube or primary peritoneal cancer (Item 73295) to expand the testing population to include patients with HER2-negative disease with mBC who have received prior (neo)adjuvant chemotherapy.

1.3 Listing was requested on the basis of a cost-utility analysis versus chemotherapy. The key components of the clinical issue addressed by the submission are presented in Table 1.

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

Component	Description
Test population	Patients with HER2-negative disease with mBC who have received prior (neo)adjuvant chemotherapy
Population	Adult patients with HER2-negative metastatic breast cancer with a confirmed germline *BRCA* mutation who have not received chemotherapy in the metastatic setting (includes patients with HER2-negative de novo metastatic disease). Clarification was provided by the sponsor during the evaluation, see paragraph 1.4.
Intervention	Germline *BRCA* mutation test Olaparib (300 mg, twice daily, orally, until progression)
Comparator	No testing and SoC (chemotherapy)
Outcomes	Progression Free Survival, Overall Survival, Health-Related Quality of Life (HRQoL)
Clinical claim	Olaparib demonstrates superior efficacy and non-inferior safety when compared to chemotherapy in HER2-negative mBC patients with a *BRCA1* or *BRCA2* mutation

Source: Table 1.1, p21 of the submission.
BRCA = Breast Cancer susceptibility gene; HER2 = human-epidermal growth factor receptor 2; HRQoL = health related quality of life; mg = milligram; mBC = metastatic breast cancer; SoC = standard of care

1.4 The sponsor clarified the proposed population during the evaluation to include the following two populations:

- Population 1 (no prior chemotherapy for mBC) includes patients who receive chemotherapy (anthracycline/taxane) in an early disease setting (neoadjuvant or adjuvant) prior to progressing to the metastatic disease setting; and
- Population 2 (de novo mBC) includes patients who have metastatic disease at time of first diagnosis. This population still require some form of chemotherapy (anthracycline/taxane) prior to receiving olaparib treatment in order to remain in line with the TGA indication. The submission suggested that clinicians would appreciate the flexibility to initiate treatment with olaparib in de novo patients without the need to first prescribe chemotherapy (see paragraph 3.6). The ESC considered that this would not be appropriate as the evidence did not support use of olaparib in patients who have not received chemotherapy in any setting.

2 Background

Registration status

2.1 The current TGA-approved product information for olaparib includes the indication in metastatic breast cancer as follows:

> As monotherapy for the treatment of adult patients who have HER2-negative metastatic breast cancer with a deleterious or suspected deleterious germline *BRCA* mutation (g*BRCA*m), for which they have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting.

Previous PBAC consideration

2.2 This was the first submission for olaparib in HER2-negative metastatic breast cancer for patients with a confirmed *BRCA1* or *BRCA2* mutation. However, olaparib was considered by the PBAC in March and November 2023 for the high risk early breast cancer (eBC) setting and was recommended for this indication in November 2023.

2.3 The submission recalled that in March 2023, the PBAC had noted that patients with de novo metastatic disease would not be able to access olaparib under the proposed listing, that cost-effectiveness had 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 (paragraph 7.18, Olaparib Public Summary Document [PSD], March 2023PBAC Meeting

Previous MSAC consideration

2.4 The MSAC PICO Advisory Sub-Committee (PASC) first considered the proposed medical service (MSAC 1507) at its November 2017 meeting. However, the application did not progress beyond PASC stage.

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

3 Requested listing

3.1 The submission's proposed wording for the restriction is shown below.

Essential elements of the requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Olaparib					
Initial: Olaparib 150mg, 100mg Tablets, 56	Published: $6,631.63 Effective: $[redacted] (submission); $[redacted] (pre-PBAC response)	2	112	5	LYNPARZA
Continuing: Olaparib 150mg, 100mg Tablets, 56	Published: $6,631.63 Effective: $[redacted] (submission); $[redacted] (pre-PBAC response)	2	112	6	LYNPARZA

Source: Table 1.6, p33 of the submission.

Requested restriction

Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
Episodicity: Not applicable
Severity: Metastatic
Condition: HER2-negative *BRCA*m breast cancer
Indication: HER2-negative *BRCA*m breast cancer
Treatment Phase: Initial treatment
Clinical criteria:
The condition must be each of: (i) negative for human epidermal growth factor receptor 2 (HER2) overexpression, (ii) metastatic disease
AND
Clinical criteria:
Patient must have a WHO status of 0, 1 or 2
AND
The condition must be associated with a class 4 or 5 *BRCA1* or *BRCA2* gene mutation
AND
Clinical criteria:
Patient must have received chemotherapy in the neoadjuvant or adjuvant setting
OR
Patient must have been diagnosed with de novo metastatic disease and received chemotherapy in the metastatic setting
AND
The treatment must be the sole PBS subsidised systemic anti-cancer therapy for this indication
AND
Patients with hormone-receptor positive breast cancer must have received at least one line of endocrine therapy (either in the adjuvant or the metastatic setting) and had disease progression during therapy, unless they had disease for which endocrine therapy was considered to be inappropriate
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
Restriction type: ☒Authority Required (Streamlined)
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have received previous PBS-subsidised treatment with this drug in the metastatic setting

AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition
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
Restriction type: ☒Authority Required (Streamlined)
Treatment Phase: Grandfathering treatment
Clinical criteria:
Patient must have received previous non -PBS-subsidised treatment with this drug in the metastatic setting
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition
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

Source: Tables 1.8, 1.9, 1.10, pp35-36 of the submission.

3.2 The submission proposed an effective price of $[redacted] (AEMP) for one pack of 56 tablets. In November 2023, the PBAC recommended the PBS listing of olaparib for certain patients with HER2-negative eBC. The pre-PBAC response proposed a revised AEMP of $[redacted], which was higher than the price in the HER2-negative eBC setting ($[redacted]).

3.3 Olaparib is intended to be used as monotherapy in this indication. The recommended dose of olaparib is 300 mg (two 150 mg tablets) taken orally twice daily, for a total daily dose of 600 mg. A 100 mg tablet is also available should dose reductions be required.

3.4 The proposed PBS listing for initial treatment includes a maximum quantity of two 56 tablet blister packs (112 tablets, sufficient for 28 days of treatment) and five repeats, equivalent of 24 weeks of treatment. The submission proposed six repeats for continuing treatment, corresponding to 28 weeks of treatment. The PBAC noted that this was consistent with the continuing listing for olaparib in eBC, where treatment is limited to 52 weeks, however the PBAC considered five repeats for continuing treatment would be appropriate in the mBC setting, as treatment would be continued until disease progression.

3.5 The submission requested an Authority Required (telephone/online PBS Authorities system) listing for the Initial treatment phase, which is consistent with the recommended listing for eBC and other current olaparib listings. However, an Authority Required (STREAMLINED) listing was requested for the Continuing treatment phase, which is not consistent with the recommended listing for eBC or the majority of Continuing treatment phase listings for olaparib. The PBAC considered an Authority Required (telephone/online PBS Authorities system) would be appropriate for the Continuing treatment phase.

3.6 For patients with de novo metastatic disease, the submission asked the PBAC to consider whether the proposed eligibility criterion requiring patients to have received prior chemotherapy in the metastatic setting (based on the TGA approved indication) was necessary. The submission suggested that clinicians would prefer flexibility to be

able to initiate treatment with olaparib in de novo mBC patients without the need to first prescribe chemotherapy. The Pre Sub-Committee Response (PSCR) argued that these patients are likely to achieve similar efficacy to patients in the 'no prior chemotherapy' (for mBC) group. The ESC noted that no evidence was presented for treatment with olaparib in de novo mBC patients who had not received prior chemotherapy. The ESC considered that, consistent with the trial population and TGA indication, the restrictions should require patients to have received chemotherapy, either in the adjuvant/neoadjuvant setting, or in the metastatic setting, including patients with de novo mBC. The PBAC agreed with the ESC that the restrictions should require patients to have received prior chemotherapy (in any setting).

3.7 The proposed restriction did not prevent use of olaparib following pembrolizumab plus chemotherapy in patients with triple negative breast cancer (TNBC) and combined positive score (CPS) ≥ 10 and *BRCA*m. No evidence for use of olaparib in this population was provided in the submission. The PBAC considered this was reasonable as prior treatment with pembrolizumab is unlikely to impact on treatment outcomes for olaparib.

3.8 The proposed restriction for initial treatment did not prevent use of olaparib in patients treated with olaparib in the eBC setting, though the proposed restriction for continuing treatment excludes patients who have developed disease progression while receiving treatment with olaparib for HER2-negative *BRCA*m breast cancer. The TGA product information for olaparib states there are no data to support rechallenge with olaparib after relapse or progression on olaparib treatment, in any setting. The PBAC considered it would not be appropriate for patients to receive retreatment after use of olaparib in the eBC setting in the absence of supportive evidence, and that the initial restriction should not allow re-treatment.

3.9 The proposed restriction did not specify that a germline *BRCA* mutation was required for eligibility to olaparib, which was not consistent with the TGA-approved product information, which refers to HER2-negative mBC with a deleterious or suspected deleterious g*BRCA*m. The ESC noted that the OlympiAD study only included patients with germline *BRCA*m and considered it would be appropriate for the restriction to specify confirmation of a class 4 or 5 germline *BRCA* variant. The PBAC noted that the listing in eBC does not specify the *BRCA* mutation is germline and considered it was reasonable for the mBC listing to be consistent with the eBC listing with respect to *BRCA* testing. The PBAC noted advice from the Secretariat that "variant" is the preferred terminology and considered it would be appropriate the criterion to include 'variant' in place of 'mutation'.

3.10 The submission proposed listing of olaparib for patients with g*BRCA*m including both de novo and recurrent mBC. The submission claimed there was a clinical need for olaparib in both patient groups, noting that the recommended olaparib listing in eBC is limited to patients classified as high risk and thus excludes patients not classified as such in the eBC setting. The PBAC considered this was reasonable.

3.11 The submission noted that there is currently an access program for olaparib in the metastatic setting, and it is anticipated that <500 patients will remain on the program at the time of listing. The PBAC noted that a grandfather restriction is not needed as patients currently accessing non-PBS treatment should be eligible to meet all criteria defined in the initial restrictions.

3.12 As a streamlined codependent submission, the submission also proposed a revision to MBS item 73295 (see underlined text of Table 2) for the medical service of germline *BRCA*m testing to determine the presence of *BRCA1* or *BRCA2* pathogenic gene variants in a patient with metastatic breast cancer who has received prior (neo)adjuvant chemotherapy, requested by a specialist or consultant physician, to determine eligibility for olaparib under the PBS. The application (MSAC 1507.1) is scheduled for MSAC consideration in August 2024. Under the proposed MBS item descriptor only patients with HER2-negative metastatic breast cancer who have received prior (neo)adjuvant chemotherapy would be eligible for the MBS item. The PBAC noted that revision of the MBS item remained for MSAC consideration, but considered that it should align with the PBS restriction population to include patients with de novo mBC as well as those who have progressed to metastatic disease following diagnosis with eBC.

Table 2: Requested MBS item descriptors

Category 6 – Pathology Services	
MBS item 73295	**Group P7 – Genetics**
Detection of germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants, in a patient with: • advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible; or • <u>HER2-negative metastatic breast cancer who *has* ~~have~~ received prior (neo)adjuvant chemotherapy</u> • triple negative early breast cancer; or • hormone receptor positive, HER2-negative, early breast cancer with at least one of the following high-risk characteristics: o tumour histological grading of at least 3; or o tumour size of greater than 2 cm; or o one or more axillary lymph node metastases requested by a specialist or consultant physician, to determine eligibility for treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor under the Pharmaceutical Benefits Scheme (PBS) Maximum of one test per patient's lifetime.	
Fee: $1,200.00 Benefit: 75% = $900.00 85% = $1,106.80*	
Explanatory note PN.0.27 Patients who are found to have any form of affected allele should be referred for post-test genetic counselling as there may be implications for other family members. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist.	

Source: Table 1.7, p34 of the submission.
MBS = Medicare Benefits Scheme
* 85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of $93.20. All out-of-hospital Medicare services that have an MBS fee of $621.50 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
Underlined text indicates proposed amendment
Source: Table 1.7, p34 of the submission

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. Breast cancer has traditionally been divided into three subtypes. These subtypes can be HR+, HER2+ or TNBC. Breast cancers that do not have oestrogen receptors (ER), progesterone receptors (PgR) or HER2 are called TNBC. TNBC tumours are typically more aggressive, difficult to treat and more common among younger women diagnosed with breast cancer (National Breast Cancer Foundation 2022). The majority of breast cancers are HER2-negative (80%-85%), based on histological subtypes (Morey 2016), and approximately 15% are also HR negative i.e., triple negative (Chan 2019, Wen 2020). Approximately 60% of breast cancers are HER2 negative and HR positive and respond to endocrine therapy. However, after progression on endocrine therapy, options for therapy are limited.

4.2 Olaparib is an oral inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3). The submission stated that olaparib binds to the active site of DNA-associated PARP and prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA double-strand breaks. In cancers that lack functional components of HRR, such as *BRCA1* or *BRCA2*, DNA double-strand breaks cannot be repaired accurately or effectively. Instead, alternative and error-prone pathways are activated, such as the non-homologous end joining pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells.

4.3 The submission proposed a revision to MBS item 73295 for the medical service of germline *BRCA*m testing to determine the presence of *BRCA1* or *BRCA2* pathogenic gene variants to determine eligibility for olaparib for mBC under the PBS (see paragraph 3.12).

4.4 The positioning of olaparib as a treatment for mBC as stated by the submission was immediately after CDK4/6i and endocrine therapy for HER2-negative/HR+ patients; and in the first line for TNBC patients. This was based on the results of a subgroup analysis from the OlympiAD trial which suggested that patients who had not received chemotherapy in the metastatic setting prior to treatment with olaparib received the most benefit in terms of PFS and OS. The ESC considered the positioning of olaparib throughout the submission was inconsistent with regard to requirements for previous chemotherapy. The requested restriction was not consistent with the requested population as described in the submission, nor the populations modelled in the economic evaluation. The ESC noted that no evidence were available to support use of olaparib in chemotherapy-naïve patients and considered that, consistent with the trial population and TGA indication, the restrictions should require patients to have

received chemotherapy, either in the adjuvant/neoadjuvant setting, or in the metastatic setting, including patients with de novo mBC.

4.5 The ESC considered that it was not reasonable for the submission's clinical evidence base and economic model to exclude patients who had been treated with chemotherapy in the metastatic setting as these patients were included in the OlympiAD trial and were not excluded from treatment under the proposed restrictions. The pre-PBAC response stated that whilst the 'no prior chemotherapy' subgroup is the patient population which derives the greatest treatment benefit in terms of OS from olaparib, the sponsor recognised the unmet need for treatment options for all *BRCA* patients. The PBAC agreed with ESC that it was appropriate for the clinical place for olaparib to be in mBC patients who have received prior chemotherapy (in either the early or metastatic setting). The PBAC welcomed the sponsor's proposal in the pre-PBAC response to revise the positioning of olaparib to reflect the pivotal clinical data, and for the ITT population of OlympiAD to inform the economic model. The PBAC also considered it was appropriate for the broader patient population to be reflected in the financial estimates.

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

5 Comparator

5.1 The nominated test comparator is no test. The ESC considered this was reasonable.

5.2 The pre-PBAC response proposed the place in therapy for olaparib as follows:

- In patients who have received chemotherapy (anthracycline/taxane) in an early disease setting (neoadjuvant or adjuvant) prior to progressing to metastatic disease setting, olaparib will be used as first line (1L) prior to treatment with chemotherapy; and
- In de novo mBC (metastatic disease at time of first diagnosis) patients are required to receive chemotherapy (anthracycline/taxane) as 1L treatment for mBC and subsequently should receive (second line) 2L olaparib treatment.

5.3 The submission's nominated drug comparator was standard of care, which the submission claimed was chemotherapy. The pivotal OlympiAD trial enrolled patients between 2014-2015 and was first published in 2017. At the time of PASC consideration in December 2017, it was noted that capecitabine, vinorelbine and eribulin were commonly used agents, and corresponded to the chemotherapies permitted in the control arm of the pivotal clinical trial (OlympiAD). The ESC considered standard of care was a reasonable comparator, but chemotherapy may not be the most representative treatment for standard of care in the proposed populations. Newer treatment options have become standard of care for certain subgroups of mBC patients, as discussed below.

5.4 The submission claimed that currently in the HR+ population, treatment with CDK 4/6 inhibitors (e.g. abemaciclib, palbociclib, ribociclib) in combination with endocrine

therapy is the standard of care. Upon progression, treatment moves to chemotherapy, or, less commonly in Australia, to everolimus with exemestane, or fulvestrant in the second line, and olaparib would be an option in this line of therapy. This was not consistent with the European Society of Medical Oncologists (ESMO) guidelines (Curgliano 2023[1], p1481) which recommend at least two lines of endocrine therapy before initiating chemotherapy, and do not recommend chemotherapy directly after first line CDK 4/6 inhibitors for patients not at risk of imminent organ failure. The American Society of Clinical Oncologists (ASCO) guideline recommendations (Al Sukhun 2024) are generally consistent with those from ESMO. The PSCR stated that treatment would include one or two lines of endocrine therapy depending on whether the clinician has deemed the patient refractory to endocrine therapy. The ESC agreed with the commentary that chemotherapy is not the standard of care after progression with first line CDK 4/6 inhibitors unless the patient is at risk of imminent organ failure (visceral crisis). Instead, a second line of endocrine therapy is the standard of care and would be the comparator for olaparib in these patients. The submission also noted that a small contingent of HR+ patients may receive first line chemotherapy, if they are in visceral crisis.

5.5 For patients with TNBC, pembrolizumab plus chemotherapy is used in patients with a CPS score (a marker of PD-L1 status) of 10 or above[2], otherwise single agent chemotherapy is given in the first line. The submission proposed that olaparib may be an option in this line of therapy. The PSCR noted that only a small proportion of patients have CPS ≥ 10, and many would receive pembrolizumab for TNBC in the early disease setting. The ESC noted that, for patients with TNBC and CPS ≥ 10, NCCN guidelines recommend pembrolizumab as the preferred 1L treatment, and olaparib would be used subsequently, as 2L for this subset of TNBC patients. As such pembrolizumab is unlikely to be a relevant comparator for olaparib.

5.6 In TNBC, the submission considered that the first line of therapy currently reimbursed is chemotherapy (alone) for the majority of patients where the current chemotherapy regimens are usually a taxane (e.g., paclitaxel or nab-paclitaxel or docetaxel) or carboplatin or doxorubicin as monotherapy or combinations of carboplatin + gemcitabine, doxorubicin + cyclophosphamide, or epirubicin + cyclophosphamide. The 2L chemotherapies used as the comparator in the pivotal OlympiAD trial (capecitabine, vinorelbine and eribulin) may not represent those used in current Australian practice.

[1] Curigliano et al (2023). ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023, https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline.

[2] In March 2023, the PBAC recommended the listing of pembrolizumab for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥10). (https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2023-03/files/pembrolizumab-mtnbc-psd-03-2023.pdf)

5.7 In patients with de novo mBC, at least one line of chemotherapy must be used before patients can be eligible for olaparib based on the requested restriction and TGA approved indication. In this case, olaparib will become a 2L therapy. The commentary stated that in patients with de novo TNBC who have failed 1L chemotherapy (with or without pembrolizumab, depending on CPS), sacituzumab govitecan may be used[3]. The PSCR noted that eligibility for sacituzumab govitecan requires at least two lines of prior systemic therapy. Therefore, for de novo metastatic TNBC, olaparib could be used in the 2L setting, where chemotherapy is the relevant comparator, or the 3L setting, where sacituzumab govitecan would be a valid comparator. For patients with recurrent TNBC and CPS < 10 olaparib would be used as 2L treatment in the metastatic setting, where sacituzumab govitecan would be a relevant comparator for patients who have received at least one line of systemic therapy in the eBC setting.

5.8 Following treatment with sacituzumab govitecan, chemotherapy remains the mainstay of treatment for triple negative patients. While not explicitly stated by the submission, it is plausible that olaparib may be used in this line of therapy (i.e. after pembrolizumab plus chemotherapy and sacituzumab govitecan, as third line therapy) in which case, chemotherapy may be the relevant comparator.

5.9 The PBAC agreed with the ESC that overall, given the evolution of treatment options in recent years, the proposal to use chemotherapy as the proxy for standard of care for all patients eligible for olaparib under the proposed PBS listing was likely unreasonable. The ESC considered that for a proportion of patients relevant comparators would include: 2L endocrine therapy (after CDK 4/6 inhibitors and endocrine therapy) and sacituzumab govitecan (as 3L therapy in de novo TNBC or 2L in recurrent TNBC). In addition, the ESC considered that the chemotherapies included as the comparator in the clinical evidence did not necessarily represent the best choice of regimen for patients with *BRCA*m mBC, which would include a platinum-based chemotherapy.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the patient preference for targeted therapies and the advantage to patients of using an oral drug rather than IV chemotherapy. The clinician noted that adverse events can be managed in clinical practice as clinicians are well-experienced in using olaparib in other

[3] In March 2022, the PBAC recommended the listing of sacituzumab govitecan for the treatment of patients with unresectable locally advanced or metastatic TNBC who have received at least two prior therapies. (https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2022-03/files/sacituzumab-govtecan-psd-march-2022.pdf).

indications. The clinician noted that there was a patient group who are likely to benefit from treatment with olaparib, but who are not currently eligible for PBS-funded treatment and many are self-funding olaparib, at substantial cost. The clinician described a patient who had a good ongoing response to olaparib and was able to stay on treatment for an extended period of 4 years, giving her additional progression-free time. The clinician noted the OlympiAD trial was initiated 10 years ago, meaning that there are now other treatments available as comparators, but that it is the best available evidence and is the basis of consensus guidelines. The clinician noted that although a statistically significant OS was not demonstrated, the trial was not powered to demonstrate OS and the availability of other treatments, including cross-over to PARP inhibitors makes it difficult to assess the OS benefit. The clinician considered that the results of the subgroup of patients without prior chemotherapy in the metastatic setting were meaningful in considering treatment choices for patients and there is a preference for treating with olaparib as early as possible to maximise benefit.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with olaparib as superior to chemotherapy in terms of efficacy and tolerability and noted the benefit of an oral treatment in allowing patients to travel, without need to return to hospital for chemotherapy infusion. The comments also noted the equity concern for patients with metastatic disease, who are currently not eligible for PBS subsidised access to olaparib.

6.3 The PBAC noted the advice received from So Brave in support of the submission, highlighting the need for advancements in treatments and access for patients to targeted treatments that can provide hope of prolonged survival and quality of life. Similarly, advice from Pink Hope supported the olaparib submission. The PBAC noted the advice from Pink Hope regarding the high need in patients with *BRCA* pathogenic variants, who often experience poorer health outcomes due to generations of cancer and cancer risk in the same family, creating additional financial and emotional burdens. Advice also focussed on the particularly high need for patients with metastatic breast cancer to have timely access to effective targeted treatments, noting that patients with early breast cancer are now able to access olaparib on the PBS. Advice from Breast Cancer Network Australia (BCNA) also supported the olaparib submission, noting that the OlympiAD trial showed an improvement in outcomes for patients treated with olaparib compared with chemotherapy. BCNA also noted equity concerns regarding affordable access to olaparib for patients with metastatic breast cancer. Both BCNA and So Brave also noted the importance of funded access to *BRCA* testing for patients with breast cancer.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the olaparib submission, categorising it as one of the therapies of “high priority for

PBS listing" on the basis of the OlympiAD trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for olaparib, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[4], based on a comparison with chemotherapy.

Clinical trial

6.5 The submission was based on one trial, OlympiAD, an open label randomised controlled trial which compared olaparib (n=205) to chemotherapy (n=97) in patients with a confirmed deleterious or suspected deleterious germline *BRCA* mutation and HER2–negative mBC, and who had received no more than two previous chemotherapy regimens for metastatic disease. Patients had been previously treated with chemotherapy (including anthracycline (unless it was contraindicated) and a taxane) in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone-receptor–positive breast cancer had received at least one endocrine therapy (adjuvant therapy or therapy for metastatic disease) and had had disease progression during therapy, unless they had disease for which endocrine therapy was considered to be inappropriate.

6.6 Results from three data cut-offs (DCO) were reported: the Primary PFS DCO on 9 December 2016 (at around 230 PFS events, median follow-up 14.1-14.5 months), the final overall survival (OS) DCO on 25 September 2017 (at around 190 OS events, median follow-up 15.5-18.9 months) and the Extended OS DCO on 17 November 2019 (included longer follow-up of patients previously censored at final OS DCO, although median follow-up was unchanged at 15.5-18.9 months).

6.7 Results were presented for the full analysis set (FAS) (N=302) which included all patients who were randomised into the study, regardless of treatment actually received. The safety analysis set (N=296) included all patients who received at least one dose of randomised study drug.

6.8 Details of the key publications of OlympiAD presented in the submission are provided in Table 3.

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

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
OlympiAD	Clinical Study Report: A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to Assess the Efficacy and Safety of Olaparib Monotherapy Versus Physician's Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients with Germline *BRCA1/2* Mutations.	7 June 2017
	Clinical Study Report Addendum 1: A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to Assess the Efficacy and Safety of Olaparib Monotherapy Versus Physician's Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients with Germline *BRCA1/2* Mutations – Final Analysis of Overall Survival and Safety Update.	6 February 2018
	•Clinical Study Report Addendum 2: A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to Assess the Efficacy and Safety of Olaparib Monotherapy Versus Physician's Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients with Germline *BRCA1/2* Mutations – Extended Overall Survival Analysis.	1 June 2020
	Robson, M., Im S.-A.; Senkus E., et al. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation.	N*EJM* 2017; 377(6): 523-533.
	Robson M.E., Im S.-A., Senkus E., et al. OlympiAD: Phase III trial of olaparib monotherapy versus chemotherapy for patients (pts) with HER2-negative metastatic breast cancer (mBC) and a germline *BRCA* mutation (g*BRCA*m).	*Journal of Clinical Oncology* 2017; 35(15 Supplement 1).
	Robson M., Ruddy K.J., Im S-A, et al. OlympiAD: Health-related quality of life (HRQoL) in patients with HER2-negative metastatic breast cancer (mBC) and a germline *BRCA* mutation (g*BRCA*m) receiving olaparib monotherapy vs standard single-agent chemotherapy treatment of physician's choice (TPC).	*Annals of Oncology* 2017; 28(Supplement 5):v96.
	Delaloge S., Conte P.F., Im S.-A., et al. OlympiAD: Further efficacy outcomes in patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation receiving olaparib monotherapy vs standard single-agent chemotherapy treatment of physician's choice.	*Annals of Oncology 2017; 28(Supplement 5):v77*
	Robson M., Ruddy K.J., IM S.-A., et al. Patient-reported outcomes in patients with a germline *BRCA* mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial.	*European Journal of Cancer 2019; 120:20-30.*
	Robson M.E., Tung N., Conte P., et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline *BRCA* mutation and HER2-negative metastatic breast cancer.	*Annals of Oncology 2019; 30(4):558-566.*
	Im S.-A., Xu B., Li W., et al. Olaparib monotherapy for Asian patients with a germline *BRCA* mutation and HER2-negative metastatic breast cancer: OlympiAD randomized trial subgroup analysis.	*Scientific reports 2020; 10(1):8753.*
	Robson M.E., Im S.-A., Senkus E., et al. OlympiAD extended follow-up for overall survival and safety: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline *BRCA* mutation and HER2-negative metastatic breast cancer.	*European Journal of Cancer 2023; 184:39-47.*
	Senkus E.; Delaloge S.; Domchek S.M., et al. Olaparib efficacy in patients with germline *BRCA*-mutated, HER2-negative metastatic breast cancer: Subgroup analyses from the phase III OlympiAD trial.	*International Journal of Cancer 2023; 153(4):803-814.*

Source: Table 2.3, p42 of the submission.

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

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Olaparib versus SoC						
OlympiAD (ITT)	302	R, OL, 14-19 months[c]	Low [a]	*BRCA* mutation HER 2-, who received no more than two previous chemo regimens for metastatic disease	OS, PFS	OS, PFS1, PFS2
OlympiAD (no prior chemo subgroup)	87	R, OL	High [b]	*BRCA* mutation HER 2-, who received no prior chemo regimens for metastatic disease	OS, PFS	OS, PFS1, PFS2

Source: pp44-50 of the submission.

HER2 – human epidermal growth factor receptor type 2; ITT = intention to treat; OL = open label; OS = overall survival; PFS1 = progression-free survival; PFS2 = time to second progression or death; R = randomised; SoC = standard of care.

a primary outcome of PFS was based on blinded review and secondary outcome of OS unlikely to be affected by open label status

b high risk of bias due to imbalances between baseline characteristics, small sample size and lack of statistical adjustment for subgroup analysis

c duration of follow-up for the no prior chemotherapy subgroup (Final OS analysis) was 22.1 months in the olaparib arm and 14.1 months in the chemotherapy arm

6.10 The ESC considered that the age and performance status of patients in OlympiAD is not expected to be substantially different from the Australian population for the proposed listing. However, the ESC noted that the chemotherapies used in the BSC arm of OlympiAD (physician's choice of capecitabine, eribulin or vinorelbine) may not be reflective of the chemotherapy regimens used in Australia, particularly for 1L TNBC (see paragraph 5.6) and did not represent the best choice of regimen for patients with *BRCA*m mBC. For patients who had progressed following treatment including an anthracycline and a taxane (as in OlympiAD), the most appropriate regimen would include a platinum-based chemotherapy. The PBAC agreed with the ESC that this applicability issue is likely to have resulted in an overestimate of the clinical benefit for olaparib in clinical practice.

6.11 In the OlympiAD trial, 38 of 302 patients in the whole trial population had de novo mBC (12.6%). This included both HR+ and TNBC patients. There were inconsistencies between the OlympiAD trial and available local registry information in the estimates of the proportion of patients diagnosed with de novo metastatic disease, which may affect applicability as well as have implications for the utilisation and financial estimates. While the proportion of de novo patients in OlympiAD was consistent with the March 2023 olaparib for eBC submission, which claimed that patients with de novo metastatic disease was roughly 5% to 15% of *BRCA*-positive patients in Australia (paragraph 2.7, olaparib PSD, March 2023 PBAC meeting); this proportion differed to the registry data relied upon by the submission for the financial estimates, which used the average of:

- The Kisqali Access Registry for Metastatic Breast Cancer in Australia (KARMA) registry, which included patients who received first-line treatment with ribociclib and aromatase inhibitor for hormone receptor positive, HER2 negative metastatic breast cancer. The KARMA registry included 26% (42/160) de novo patients; and

- The Advanced Hormone Receptor Positive Breast Cancer (ARORA) registry analysis included: patients diagnosed with metastatic, or inoperable histologically confirmed HR+, HER2- breast cancer (either de novo metastatic or relapsed), after 1st January 2020. The ARORA registry estimated 41% (173/424) of included patients to be de novo.

6.12 The submission focused on the subgroup of patients who had not received prior chemotherapy for mBC (n=87, of whom 59 were randomised to olaparib and 28 to chemotherapy). The PSCR argued that de novo metastatic patients and those who had not received treatment in the metastatic setting were the least pre-treated and most likely to benefit from olaparib and were best aligned to the subgroup. The PSCR also stated that the results in the subgroup provide a rationale for using olaparib early in the metastatic treatment pathway.

6.13 The ESC recalled its previous advice that the pre-planned subgroup analysis of OS for patients who had not received chemotherapy for metastatic disease may have been affected by potential confounding, small sample size and lack of statistically significant OS advantage in the overall population (paragraph 2.8, olaparib PSD, March 2023 PBAC meeting).

6.14 In addition, given de novo patients and recurrent patients who have had no prior chemotherapies in the mBC setting have different disease trajectories, it was unclear that both populations being the 'least pre-treated' was sufficient grounds to use the no prior chemotherapy subgroup as a proxy for the de novo population. Additionally, based on the proposed restriction and TGA indication, de novo patients must first be treated with chemotherapy in the metastatic setting to be eligible for olaparib treatment. Consequently, the ESC considered the no prior chemotherapy subgroup in OlympiAD was not a reasonable proxy for de novo patients. The ESC considered that it was not reasonable for the submission's clinical evidence base for the clinical claim and economic model to exclude patients who had been treated with chemotherapy in the metastatic setting, as these patients comprised the majority of patients in the OlympiAD trial (71%) and were not excluded from treatment under the proposed restrictions. The ESC considered it would be more appropriate to apply the treatment effect from the whole trial population (up to two lines of prior chemotherapy in metastatic setting). The PBAC noted that the pre-PBAC response proposed a revised clinical place for olaparib (see paragraph 4.5) and accepted that the whole trial population (ITT) was the most relevant for the revised population and considered this was appropriate.

Comparative effectiveness

Progression free survival

6.15 At the time of the primary PFS analysis (9 December 2016), median PFS in the whole trial population was 2.8 months longer in the olaparib group than in the chemotherapy group and treatment with olaparib resulted in a 42% reduction in the relative risk and 13% reduction in the absolute risk at 12 months of disease progression or death

compared to chemotherapy in the whole trial population (median PFS 7.0 months vs 4.2 months; 12-month PFS 25.9% vs 15%, hazard ratio [HR] for disease progression or death 0.58; 95% confidence interval [CI] 0.43 to 0.80; p<0.001). The submission considered that this improvement in PFS was both statistically significant and clinically relevant.

6.16 The submission noted that in patients who received no prior chemotherapy for mBC, olaparib significantly extended PFS by 3.8 months and reduced the relative risk of disease progression or death by 44% compared to chemotherapy (median 7.7 vs 3.9 months; HR=0.56; 95% CI: 0.34, 0.98; p<0.05). The proportion of patients who had not progressed or died at DCO for the primary PFS analysis was 74.6% in the olaparib arm compared with 71.4% in the chemotherapy arm.

6.17 Table 5 presents the primary endpoint, PFS by BICR at the primary PFS DCO in the whole trial population as well as the no prior chemotherapy subgroup and its complement.

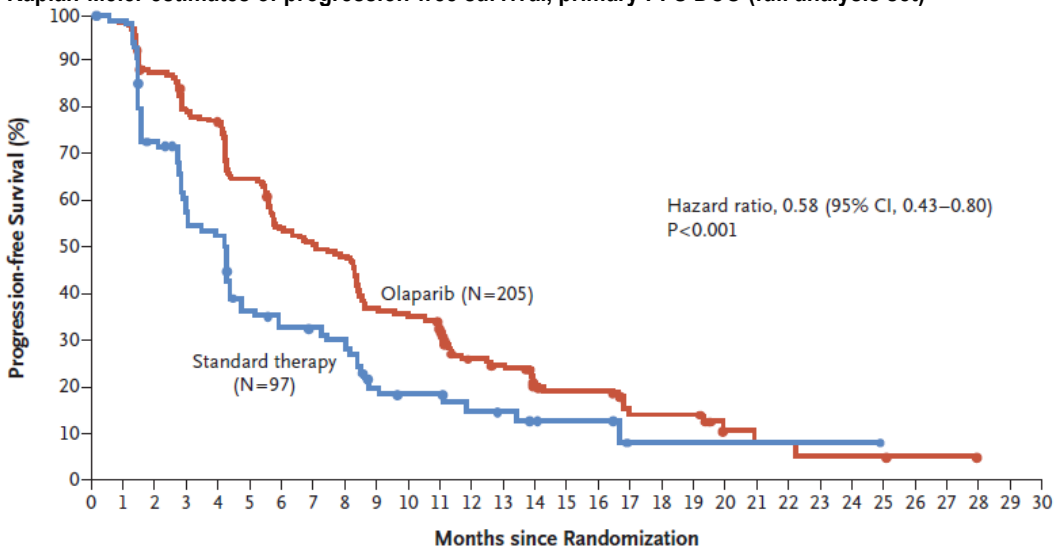
Table 5: Progression-free survival, primary PFS DCO

	Whole trial population		No prior chemotherapy for mBC		Prior chemotherapy	
	Olaparib N=205	**Chemotherapy N=97**	**Olaparib N=59**	**Chemotherapy N=28**	**Olaparib N=146**	**Chemotherapy N=69**
Number (%) of patients who had not died or progressed [a]	163 (79.5)	71 (73.2)	44 (74.6)	20 (71.4)	119 (81.5)	51 (73.9)
HR (95% CI)[b]	**0.58 (0.43, 0.80)**		0.56 (0.34, 0.98)		0.65 (0.47, 0.91)	
p-value	0.0009		NR		NR	
Median PFS (95% CI), months [c]	7.03 (5.68, 8.31)	4.17 (2.79, 4.27)	7.66 (5.45, 8.51)	3.88 (1.41, 7.95)	7.03 (5.55, 8.31)	4.17 (2.76, 4.63)
Progression-free at 6 months, %	54.1	32.9	NR			
Progression-free at 12 months, %	25.9	15.0	NR			
Median time to censoring, months [d]	13.62	4.29	13.70	6.32	11.79	3.43

Source: Table 2.15, p67 of the submission and Table 2.32, p91 of the submission.
Abbreviations: CI = confidence interval; DCO = data cut-off; HR = hazard ratio; NR = not reported; PFS = progression-free survival
Text in bold indicates statistically significant difference. Statistical significance could not be claimed in subgroups as not part of sequential hypothesis testing.
a Based on independent central review of radiological scans. Patients who had not progressed or died at the time of analysis, or who progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST assessment, or Day 1 if the patient had no evaluable visits or no baseline assessment (unless they died within 2 visits of baseline).
b A hazard ratio <1 favours Olaparib 300 mg bd. The CI was calculated using a profile likelihood approach.
c Calculated using the Kaplan-Meier technique
d Censored patients only

6.18 Figure 1 presents the Kaplan Meier (KM) curves for PFS from the primary PFS DCO analysis in the whole trial population.

Figure 1: Kaplan-Meier estimates of progression-free survival, primary PFS DCO (full analysis set)



No. at Risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

Source: Figure 2.4, p67 of the submission.
CI = confidence interval, DCO = data cut-off

Overall survival

6.19 OS results from the final OS DCO and extended OS DCO for the whole trial population of OlympiAD, the no prior chemotherapy subgroup and its complement are presented in Table 6 and Table 7, respectively.

6.20 As of the final OS DCO, the OS whole trial data had reached 64% maturity, with 192 events (130 patients had died in the olaparib arm, and 62 in the chemotherapy arm). As of the DCO for the extended OS analysis, OS data had reached 76.8% maturity, with a further 40 events (total 159 deaths in the olaparib arm and 73 deaths in the chemotherapy arm).

6.21 In the whole trial population, no significant difference in the median OS was observed between the olaparib and the chemotherapy arms at either DCO. The CSR for the extended OS analysis noted that all efficacy analyses are exploratory, and all p-values are nominal. The pre-PBAC response noted that the OlympiAD trial was not powered to show a statistically significant benefit in the secondary endpoint of OS.

6.22 In the final OS analysis for the no prior chemotherapy subgroup, the OS benefit was numerically greater than in the olaparib arm, where median OS was increased by 7.9 months and the risk of death reduced by 49% compared to chemotherapy (median 22.6 vs 14.7 months; HR = 0.51; 95%CI: 0.29, 0.90). In the extended OS analysis for the no prior chemotherapy subgroup, the OS benefit remained numerically greater in the olaparib arm, with the difference in median OS remaining at 7.9 months and the relative risk of death reduced by 45% and the absolute risk of death at 24 months reduced by 21% compared to chemotherapy (median 22.6 vs 14.7 months; survival at 24 months 48% vs 27%, HR=0.55; 95% CI: 0.33, 0.95). The submission argued this was

clinically relevant given the recommended minimal clinically relevant difference (MCID) of 4.5 to 6 months derived by consensus of working groups convened by the Cancer Research Committee of the American Society of Clinical Oncology (Ellis 2014). In this subgroup, 40.8% of patients in the olaparib arm were alive at 3 years compared with 12.8% of patients in the chemotherapy arm.

Table 6: Median OS and log-rank test, final OS DCO (full analysis set)

	Whole trial population		No prior chemotherapy for mBC		Prior chemotherapy	
	Olaparib N=205	Chemotherapy N=97	Olaparib N=59	Chemotherapy N=28	Olaparib N=146	Chemotherapy N=69
Total number of deaths, n (%)	130 (63.4)	62 (63.9)	30 (50.8)	21 (75.0)	100 (68.5)	41 (59.4)
Median OS (95% CI), months	19.25 (17.15, 21.55)	17.12 (13.86, 21.85)	22.6 (17.8, NC)	14.7 (11.0, 21.3)	18.8 (16.3, 20.4)	17.2 (13.5, 27.2)
HR (95% CI)	0.90 (0.66, 1.23)		0.51 (0.29, 0.90)		1.13 (0.79, 1.64)	
p-value (2-sided)	0.5131		0.0218		0.5156	
Survival at 6 months, %	93.1	85.8	93.2	88.5	93.1	84.9
Survival at 12 months, %	72.7	69.2	76.0	65.4	71.4	70.8
Survival at 18 months, %	54.1	48.0	62.1	46.2	50.8	48.8
Survival at 24 months, %	NR	NR	48.0	26.9	35.0	44.1
Median follow-up for OS in all patients, months	18.92	15.54	22.05	14.14	17.40	16.76
Median follow-up for OS in censored patients, months	25.30	26.25	25.53	26.91	25.17	25.95

Source: Table 2.19, p72 and Table 2.30, p88 of the submission.

CI = confidence interval; DCO = data cut-off; HR = hazard ratio; NC = not calculable; OS = overall survival

Note: Each subgroup analysis was performed using a single Cox proportional hazards model containing the treatment term, the subgroup covariate of interest and the treatment by subgroup interaction. A hazard ratio <1 favours Olaparib 300 mg bd. The CI was calculated using a profile likelihood approach. P-values were calculated from likelihood ratio statistics, using a contrast statement for each subgroup level.

Table 7: Median OS and log-rank test, no prior chemotherapy for mBC, extended OS DCO (full analysis set)

	Whole Trial Population		No prior chemotherapy for mBC		Prior chemotherapy	
	Olaparib N=205	Chemotherapy N=97	Olaparib N=59	Chemotherapy N=28	Olaparib N=146	Chemotherapy N=69
Total number of deaths, n (%)[a]	159 (77.6)	73 (75.3)	42 (71.2)	22 (78.6)	117 (80.1)	51 (73.9)
Median OS (95% CI), months [b]	19.25 (17.15, 21.55)	17.12 (13.86, 21.85)	22.6 (17.8, 36.7)	14.7 (11.0, 21.3)	18.8 (16.3, 20.4)	17.2 (13.5, 27.2)
HR (95% CI)	0.89 (0.67, 1.18)		0.55 (0.33, 0.95)		1.05 (0.76, 1.47)	
p-value (2-sided)	0.4167		NR		NR	
Survival at 6 months, %	93.1	85.8	93.2	88.5	93.1	84.9
Survival at 12 months, %	72.7	69.2	76.0	65.4	71.4	70.8
Survival at 18 months, %	54.1	48.0	62.1	46.2	50.8	48.8
Survival at 24 months, %	39.0	39.1	48.1	26.9	35.0	44.1
Survival at 36 months, %	30.8	25.6	40.8	12.8	22.4	24.7
Survival at 48 months, %	27.9	21.2	27.8	12.8	16.1	15.8
Survival at 60 months, %	23.8	18.1	18.6	NC	12.3	15.8
Median follow-up for OS in all patients, months	19.6	14.8	22.05	14.14	17.40	16.76
Median follow-up for OS in censored patients, months	16.9	14.8	49.81	28.11	48.00	31.72

Source: Table 2.20, p74 and Table 2.31, p90 of the submission.
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; NC = not calculable; NR = not reported; OS = overall survival
a Overall survival is defined as the time from the date of randomisation until death due to any cause. Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was known to be alive.
b Calculated using the Kaplan-Meier technique.

6.23 The submission argued that the OS in the whole trial comparison may have been confounded by an imbalance between treatment arms in the use of subsequent therapies following progression. Specifically, more patients in the chemotherapy arm received PARP inhibitors, platinum-based therapy, and cytotoxic chemotherapy after disease progression on the assigned treatment, compared to the olaparib arm. Subsequent PARP inhibitor use post-discontinuation was reported for 8 (8.2%) patients in the chemotherapy arm and 2 (1.0%) patients in the olaparib arm in the final OS analysis. The commentary noted the use of subsequent cancer treatments actually appeared to favour the olaparib arm in OlympiAD after accounting for continued use of study treatment after discontinuation, as 37 (18.1%) of patients in the olaparib arm at the final PFS DCO 'continued study treatment' after a protocol defined discontinuation, such that these patients were effectively using a subsequent PARP inhibitor but were not included as such. The pre-PBAC response also noted that the subsequent use of targeted biologics was also greater in the chemotherapy arm (19.6% versus 14.6%). The PBAC considered that imbalances in subsequent therapies not available in Australian clinical practice (PARP inhibitors and targeted biologics) are likely to have impacted on overall survival in OlympiAD, however the extent of impact is uncertain.

6.24 The commentary noted that although the numerical differences in OS between the olaparib and chemotherapy arms in the subgroup of patients with no prior chemotherapy in the metastatic setting at both data cuts appeared more favourable

when compared to the whole trial population and the complement, these results are highly uncertain and should not be relied upon given:

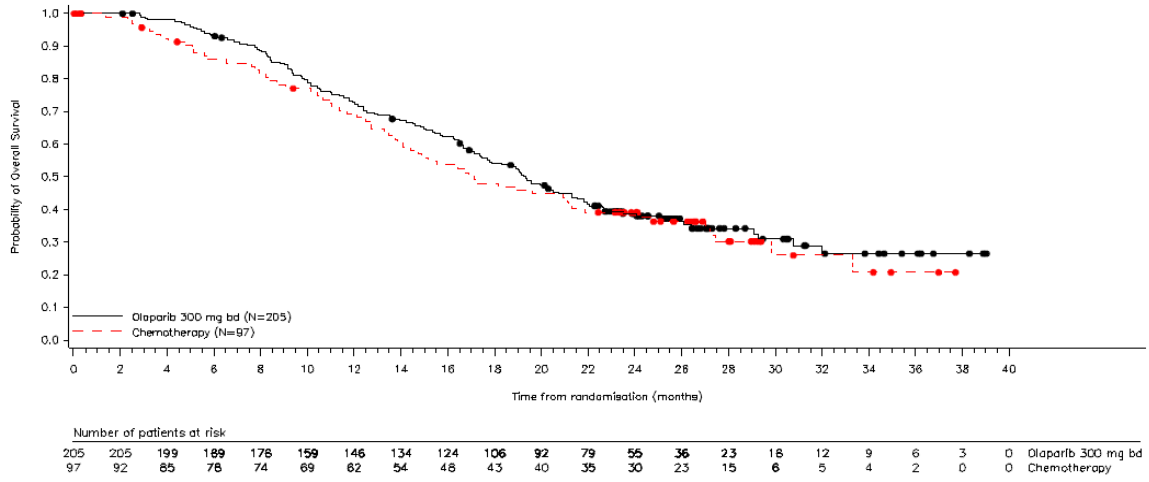
- There was a small sample size informing the subgroup analysis (Olaparib N=59; Chemotherapy N=28).
- Results were not formally tested in the trial (and not included in the trial's hierarchical hypothesis testing strategy).
- The larger median OS difference between treatment arms in the no prior chemotherapy subgroup was driven by both longer olaparib OS (22.6 months) and shorter chemotherapy OS (14.7 months) when compared the whole trial population (19.25 and 17.12 months for olaparib and chemotherapy respectively). As such, OS in the chemotherapy arm of the no prior chemotherapy subgroup may be underestimated.
- There were baseline imbalances (e.g. performance status, number of metastatic sites) that likely favoured olaparib and may have contributed to the observed OS difference in the no prior chemotherapy subgroup.
- There was little difference between the point estimate for the PFS hazard ratio (HR) in the no prior chemotherapy subgroup (PFS HR 0.56, 95% CI 0.34, 0.98) compared to the whole trial population (PFS HR 0.58, 95% CI 0.43, 0.80) or the complement subgroup (PFS HR 0.65, 95% CI 0.47, 0.91), suggesting that this was not a mechanism by which any additional OS benefit was derived.

6.25 The PSCR argued that results in the LUCY trial[5] (an open-label, single-arm study of olaparib in patients with *BRCA*m HER-2 negative mBC after prior chemotherapy) supported the finding of a greater OS benefit for the subgroup of patients with no prior chemotherapy in the metastatic setting. However, LUCY was a single arm trial and therefore supports a longer OS for the subgroup, but not a greater OS benefit over chemotherapy. Overall, the ESC considered that the shorter OS for the BSC arm in the subgroup and the lack of difference in PFS between the groups strongly suggested that the results in the subgroup were not a reliable basis for determining the population of patients most likely to benefit from olaparib, for supporting the clinical claim of OS benefit, or for informing the level of clinical benefit in the economic model. The PBAC noted that the pre-PBAC appropriately revised the basis of the economic model to the clinical data for the ITT population.

6.26 Figure 2 and Figure 3 present the KM curves for OS at the final and extended OS DCO analyses for the whole trial population.

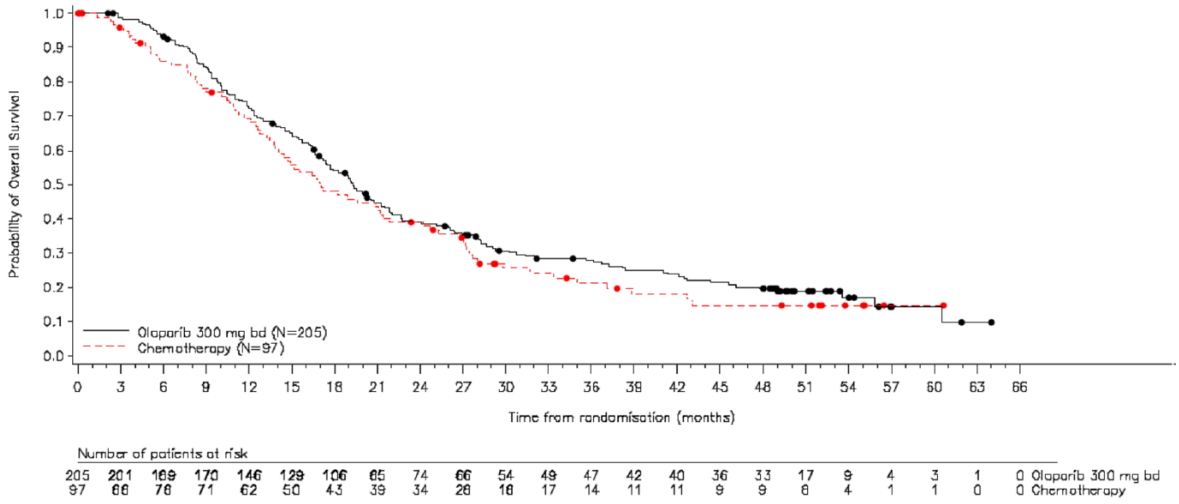
[5] Balmaña, J., Fasching, P.A., Couch, F.J. *et al.* Clinical effectiveness and safety of olaparib in BRCA-mutated, HER2-negative metastatic breast cancer in a real-world setting: final analysis of LUCY. *Breast Cancer Res Treat* **204**, 237–248 (2024). https://doi.org/10.1007/s10549-023-07165-x

Figure 2: Kaplan–Meier estimates of overall survival, final OS DCO (full analysis set)



Source: Figure 2.7, p72 of the submission.
Abbreviations: bd = twice daily; OS = overall survival

Figure 3: Kaplan–Meier estimates of overall survival, extended DCO (full analysis set)



Source: Figure 2.9, p74 of the submission.
bd = twice daily; DCO = data cut-off; OS = overall survival

Time to second progression (or death)

6.27 Table 8 presents the results of time to second progression (or death) (PFS2) in the whole trial population at the primary PFS DCO. The submission considered that based on these results, a continued benefit beyond first progression was demonstrated, with olaparib providing a statistically significant and clinically meaningful delay in the time to second progression or death (HR=0.57, 95% CI: 0.40, 0.83; p=0.0017). PFS2 results would be influenced by subsequent cancer therapy (see paragraph 6.23). The pre-PBAC response noted that in the ITT population the benefits of olaparib seemed to be conferred to subsequent lines of therapy. Time to first subsequent treatment (TFST) in the olaparib arm was 9.4 months vs 4.3 months in the TPC arm; time to second subsequent treatment (TSST) was 14.3 months vs 10.5 months; PFS2 (time to second

progression) in olaparib arm was 13.2 months vs 9.3 months in TPC which indicates that benefit from olaparib extends beyond the end of therapy.

6.28 The submission noted that there was no further analysis of PFS2 at the time of the final or extended OS analyses since statistical significance was shown for PFS and PFS2 at the primary analysis.

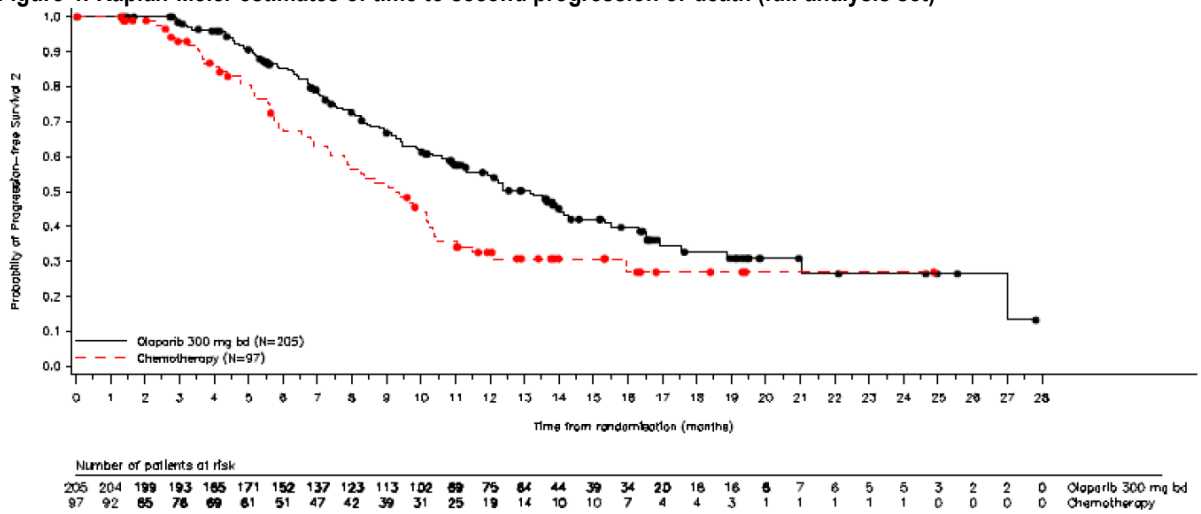
Table 8: Time to second progression or death, log-rank test, primary DCO (full analysis set)

Analysis	Olaparib N=205	Chemotherapy N=97
Number (%) of events [a]	104 (50.7)	53 (54.6)
Median PFS2 (95% CI), months [b]	13.17 (10.94, 15.34)	9.26 (7.29, 10.35)
HR (95% CI)	0.57 (0.40, 0.83)	
P-value (2-sided)	0.0033	
PFS2 at 6 months, %[b]	85.3	68.4
PFS2 at 12 months, %[b]	54.7	32.6
Median follow-up for PFS2, months [c]	11.79	9.71

Source: Table 2.18, p71 of the submission.
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; PFS2 = time to second progression or death
a Patients who had not had a second disease progression or died at the time of analysis, or who had second progression or died after 2 or more missed visits, were censored at the latest evaluable assessment where they were known to be alive and without a second disease progression
b Calculated using the Kaplan-Meier technique
c Censored patients only

6.29 Figure 4 presents the KM results for PFS2 in OlympiAD in the whole trial population.

Figure 4: Kaplan-Meier estimates of time to second progression or death (full analysis set)



Source: Figure 2.6, p71 of the submission.
Bd = twice daily

Health-related quality of life

6.30 The submission discussed results of global health-related quality of life (HRQoL) evaluated based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item module (EORTC QLQ C3). This outcome was not formally tested and as such the p-values should be interpreted with caution. Additionally, as this was an open-label study design with patients being aware of their

treatment arm allocation, the patient reported outcome results are less robust. After the first year (from Visit 24 onwards), EORTC QLQ-C30 compliance fell below 50% at some visits in both treatment arms and therefore the results are more uncertain after this time point.

6.31 The mean score on the QLQ-C30 at baseline was 63.2 (SD=21.0) in the olaparib arm and 63.3 (SD=21.2) in the chemotherapy arm. The adjusted mean change from baseline across all time points was 3.9 (SE=1.2) in the olaparib arm (among the 191 patients who completed the questionnaire at baseline and at least once thereafter) and -3.6 (SE=2.2) in the chemotherapy arm (among 73 patients), corresponding to an estimated mean difference of 7.5 points (95% CI: 2.5, 12.4; p=0.004).

6.32 The submission claimed that the QLQ-C30 results showed a statistically and clinically significant improvement in QoL favouring olaparib treatment. Osoba 1998[6] reported a change of 5-10 points in the EORTC-QLQC30 as a small change, however statistical significance could not be concluded as QLQ-C30 was not part of the sequential hypothesis testing of OlympiAD.

6.33 In the olaparib arm, 69/205 (33.7%) patients compared with 13/97 (13.4%) patients in the chemotherapy arm showed improvement in the global health status/QoL score best overall QoL response (2 visit responses of 'improved' a minimum of 21 days apart without an intervening response of 'deterioration'). The proportion of patients with no change or deterioration (at least a 10-point decrease) was generally more favourable for the olaparib arm (41.5% no change; 11.7% deterioration) compared with the chemotherapy arm (25.8% no change; 19.6% deterioration).

6.34 The submission stated that the median time to a ≥10 point decrease in QLQ-C30 score was not reached in the olaparib arm and was 15.3 months in the chemotherapy arm (HR= 0.44; 95% CI: 0.25, 0.77; p=0.0043). However, neither arm reached 50% of patients with events. Consequently, the median time ≥ 10 point decrease could not be verified during the evaluation. The submission stated that this represents a nominally statistically significant delay in the time to HRQoL deterioration in the olaparib arm compared with chemotherapy. The EORTC-QLQC30 results from OlympiAD primary PFS DCO were used to inform the economic model.

Comparative harms

6.35 Table 9 presents a summary of key adverse events (AEs) in the whole trial population as of the final OS analysis. The submission considered that although most patients in both treatment arms reported AEs during the study, these were generally non-serious, low-grade (Grade 1 or 2) AEs which did not lead to permanent treatment

[6] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44.

discontinuation. The submission considered that this indicates that olaparib has an acceptable safety and tolerability profile for use in this treatment setting.

Table 9: Summary of AEs, final OS DCO (safety analysis set)

AE category	Number (%) of patients[a]		Risk difference (95% CI)
	Olaparib N=205	Chemotherapy N=91	
Any AE	200 (97.6)	87 (95.6)	0.02 (-0.03, 0.07)
Any AE causally related to study drug[b]	178 (86.8)	74 (81.3)	0.06 (-0.04, 0.15)
Any AE of CTCAE Grade 3 or higher	78 (38.0)	45 (49.5)	-0.11 (-0.24, 0.01)
Any AE of CTCAE grade 3 or higher, causally related to study medication[b]	50 (24.4)	31 (34.1)	-0.1 (-0.21, 0.02)
Any AE with outcome of death	1 (0.5)	0	0 (0, 0.01)
Nausea, any grade	119 (58.0)	32 (35.2)	**0.23 (0.11, 0.35)**
Anaemia[d] any grade	81 (39.5)	23 (25.3)	**0.14 (0.03, 0.25)**
Anaemia[d], Grade 3 or above	32 (15.6)	4 (4.4)	**0.11 (0.05, 0.18)**
Vomiting, any grade	66 (32.2)	14 (15.4)	**0.17 (0.07, 0.27)**
Neutropenia, any grade	37 (18.0)	28 (30.8)	**-0.13 (-0.24, -0.02)**
Palmar-plantar erythrodysesthesia, any grade	1 (0.5)	19 (20.9)	**-0.2 (-0.29, -0.12)**
Decreased neutrophil count, grade 3 or above	10 (4.9)	17 (18.7)	**-0.08 (-0.16, -0.01)**

Source: Table 2.26, p81 and Table 2.27, p83 of the submission.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; SAE = serious adverse event.
a Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.
b As assessed by the Investigator to have a reasonable possibility that the event may have been caused by the study drug.
c Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/chemotherapy. There were no other significant AEs defined for olaparib. Classified using MedDRA version 19.1. CTCAE version 4.0.
d The anaemia category includes anaemia, decreased haemoglobin level, decreased haematocrit, decreased red-cell count, and erythropenia
Text in bold indicate risk differences which did not include 0 in the 95% confidence interval
Note: Risk differences calculated during the evaluation using Microsoft Excel

6.36 AEs reported at a higher frequency (≥5% difference) with chemotherapy treatment compared with olaparib included neutropenia/neutrophil count decreased, aspartate aminotransferase increased, alanine aminotransferase increased, myalgia, alopecia, peripheral sensory neuropathy and palmar-plantar erythrodysaesthesia syndrome. Nausea, anaemia, vomiting, fatigue, cough, decreased appetite, back pain, and headache were reported at a higher frequency (≥5% difference) in the olaparib arm. Overall, risk differences in severe AEs (grade 3 or above) between the two treatments were only observed for anaemia (0.11, 95% CI 0.05, 0.18, favouring chemotherapy) and decreased neutrophil count (-0.08, 95% CI -0.16, -0.01, favouring olaparib).

6.37 Overall, the adverse events suggested a different but generally non-inferior safety profile for olaparib compared to chemotherapy.

Benefits/harms

6.38 A summary of the comparative benefits and harms for olaparib versus chemotherapy is presented in Table 10.

Table 10: Summary of comparative benefits and harms for olaparib versus chemotherapy

Events	Olaparib	Chemotherapy	Absolute Difference	HR (95% CI))
Benefits (whole trial population)				
Progression free survival (median duration of follow up 14.5 months for olaparib, 14.1 for chemotherapy)				
Progressed, n/N (%)	163 (79.5)	71 (73.2)	6.3%	0.58 (0.43, 0.80) 0.0009
Progression free at 6 months (%)	54.1	32.9	21.2%	
Progression free at 12 months (%)	25.9	15.0	10.9%	

Harms (whole trial population)						
	Events		**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
	Olaparib n/N	**Chemo n/N**		**Olaparib**	**Chemo**	
OlympiAD						
Nausea, any grade	119 (58.0)	32 (35.2)	1.65 (1.22, 2.23)	58	35	0.23 (0.11, 0.35)
Anaemia[a] any grade	81 (39.5)	23 (25.3)	1.56 (1.06, 2.31)	40	25	0.14 (0.03, 0.25)
Anaemia[a], Grade 3 or above	32 (15.6)	4 (4.4)	3.55 (1.29, 9.75)	15	4	0.11 (0.05, 0.18)
Vomiting, any grade	66 (32.2)	14 (15.4)	2.09 (1.24, 3.52)	32	15	0.17 (0.07, 0.27)
Neutropenia, any grade	37 (18.0)	28 (30.8)	0.59 (0.38, 0.9)	18	31	-0.13 (-0.24, -0.02)
Palmar-plantar erythrodysesthesia, any grade	1 (0.5)	19 (20.9)	0.02 (0, 0.17)	1	21	-0.2 (-0.29, -0.12)
Decreased neutrophil count, grade 3 or above	10 (4.9)	17 (18.7)	0.26 (0.12, 0.55)	5	19	-0.08 (-0.16, -0.01)

Source: Table 2.15, p67, Table 2.32, p91, Table 2.19, p72 and Table 2.30, p88 Table 2.20, p74 and Table 2.31, p90, and Table 2.26, p81 of the submission.

AE = adverse event; CI = confidence interval; DCO = data cut-off; PFS = progression free survival; HR = hazard ratio; NR = not reported; RD = risk difference; RR = relative risk

a The anaemia category includes anaemia, decreased haemoglobin level, decreased haematocrit, decreased red-cell count, and erythropenia

Note: Risk differences calculated during the evaluation using Microsoft Excel

6.39 On the basis of the direct whole trial population evidence presented by the submission, for every 100 patients with HER2-negative mBC with a confirmed *BRCA1* or *BRCA2* mutation who have previously received up to two lines of chemotherapy, treatment with olaparib compared with chemotherapy over a median duration of 14.5 months and 14.1 months, respectively:

- approximately 6 additional patients will remain progression-free.

6.40 On the basis of the direct whole trial population evidence presented by the submission, for every 100 patients with HER2-negative mBC with a confirmed *BRCA1* or *BRCA2* mutation who have previously received up to two lines of chemotherapy, treated with olaparib compared with chemotherapy over a median duration of 18.9 months and 15.5 months, respectively:

- approximately 23 additional patients would experience nausea;
- approximately 14 additional patients would experience anaemia;
- approximately 11 additional patients would experience Grade ≥3 anaemia;
- approximately 17 additional patients would experience vomiting;

- approximately 13 fewer patients would experience neutropenia; and
- approximately 8 fewer patients would experience a Grade ≥3 decrease in neutrophil count.

Clinical claim

6.41 The submission made the following clinical claims:

- In the whole trial population, which included patients with HER2-negative mBC with a confirmed *BRCA1* or *BRCA2* mutation who had previously received up to two lines of chemotherapy for mBC, olaparib was superior in terms of effectiveness compared with chemotherapy based on PFS and non-inferior in terms of safety compared with chemotherapy.
- In the subgroup of patients with HER2-negative mBC with a confirmed *BRCA1* or *BRCA2* mutation who had not previously received chemotherapy for mBC, olaparib was superior in terms of OS and PFS compared with chemotherapy.

6.42 With regard to the whole trial population of OlympiAD, the trial supported the claim of superior efficacy with a statistically significant improvement in PFS as well as PFS2, but not OS, even at longer follow-up. However, the treatments included in the comparator arm are unlikely to fully represent standard of care (including endocrine therapy, sacituzumab and other chemotherapy regimens). These factors reduce the applicability of OlympiAD to the Australian population and increase uncertainty of the clinical claim.

6.43 The submission's claim of superior efficacy in the subgroup of patients who received no prior chemotherapy on the basis of PFS, may be reasonable on the basis that PFS has been demonstrated in the overall population. The submission's claim of superior efficacy on the basis of improved OS was highly uncertain and may not be supported because results were not statistically significant, and treatment groups do not appear to be well-balanced in the subgroup.

6.44 With regard to the claim of non-inferior safety in the overall population, this was generally supported when compared to the three chemotherapy regimens included as comparators in OlympiAD (capecitabine, eribulin and vinorelbine). However, in the Australian setting, it would be expected that a proportion of patients would be treated with 2L endocrine therapy (for HR+ patients) or sacituzumab govitecan. Consequently, it is unlikely that the comparator safety profile in OlympiAD reflects the average safety profile for the requested treatment population. The safety claim was therefore overall uncertain.

6.45 The PBAC considered that the claim of superior comparative effectiveness was reasonable based on PFS benefit, but the magnitude of PFS benefit was uncertain as the comparator treatments are unlikely to fully represent standard of care. The PBAC also considered that the data did not clearly support an OS benefit, but noted that the trial was not powered to detect a difference in OS and imbalances in subsequent

treatments are likely to have impacted on this outcome.

6.46 The PBAC considered that the claim of non-inferior comparative safety was reasonable, but noted that there was some uncertainty as no comparison with alternative comparator treatments was presented.

Economic analysis

6.47 The submission presented a cost-utility analysis comparing olaparib with chemotherapy in patients with HER2-negative, *BRCA*m mBC who had not previously received chemotherapy in the metastatic setting based on the corresponding subgroup in the OlympiAD trial (hence referred to has the subgroup model). The submission also presented an additional cost-utility analysis reflective of the whole trial population (hence referred to as the ITT model). Recognising the unmet need for all HER2-negative, *BRCA*m mBC patients, the pre-PBAC response accepted the ITT population model structure as most appropriate for decision-making. The PBAC agreed with the pre-PBAC response and considered results for the ITT population were appropriate as the basis for the economic model.

6.48 Table 11 presents a summary of the overview, key inputs and rationale of the submission's economic evaluation.

Table 11: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Olaparib versus chemotherapy
Population	Subgroup (base case): patients with HER2-negative mBC with a confirmed *BRCA*1 or *BRCA*2 mutation who had not previously received chemotherapy for mBC. ITT: all patients in the OlympiAD trial (i.e. those who had received up to two lines of chemotherapy in the metastatic setting).
Time horizon	10 years based on median 18 months of follow-up in the Final OS analysis of OlympiAD.
Outcomes	Progression-free years gained, life-years gained, quality-adjusted life years gained
Methods used to generate results	Partitioned survival model
Health states	PFS1, PFS2, progressive disease (PD), death
Cycle length	1 month
Allocation to health states	PFS, PFS2, and OS extrapolated using parametric functions fitted directly to data from OlympiAD. Australian lifetables applied after end of trial follow-up to capture all-cause mortality observed after the trial.
Extrapolation method	In the base case model, the submission extrapolated PFS, OS and PFS2 using a lognormal parametric function in both arms. In the ITT analysis, a lognormal function was used in all extrapolated curves, except for PFS2, which utilised a generalised gamma function in both arms.
Health related quality of life	EORTC QLQ-C30 scores from OlympiAD were mapped to EQ-5D-5L based utility values using published mapping algorithms, and the literature for the progressed disease state. The health state utilities were PFS1-0.817 for olaparib and 0.745 for chemotherapy; PFS2 0.749 for olaparib and 0.717 for chemotherapy; PD 0.53 for both treatments.
BRCA test modelling	Though *BRCA* test costs are incorporated into the model, the prevalence of *BRCA*m was not considered, which underestimated the number of tests required for each patient treated.

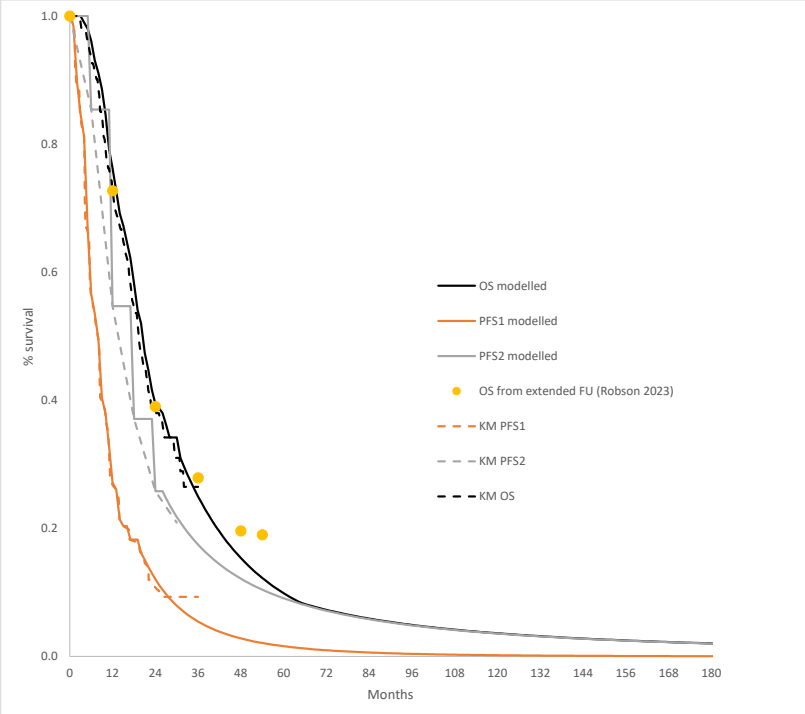
Source: Table 3.1, p104 of the submission.
EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item module; EQ-5D5L = EuroQoL 5 dimension 5 level; OS = overall survival; PFS= progression free survival; PFS2 = time to second progression or death

6.49 Though the submission base case included a 10 year time horizon, the submission argued that a 15-year time horizon could be permitted due to the young baseline age (45 years), the robustness/maturity of OlympiAD OS data which reduces the level of uncertainty in the model, and the availability of effective later line treatments (such as SG for TNBC patients). The evaluation noted that a 10-year time horizon was consistent with the model for pembrolizumab plus chemotherapy for TNBC. The ESC considered the 10-year time horizon was reasonable. The pre-PBAC response maintained that a 15 year time horizon was reasonable, but accepted application of 10 years in its revised base case.

6.50 The transition probabilities were estimated by fitting a series of parametric survival models to patient-level time-to-event data. For PFS1, PFS2 and OS, the point of truncation was set at the point at which approximately 10% of patients remain in the risk set. The submission considered this was consistent with the model for pembrolizumab in mBC (March 2023 PBAC meeting), and methodology presented in Pocock 2002. The ESC had previously considered that where 10% of the cohort remain at risk may be considered the minimum required to accept reliability of the KM curves (paragraph 6.48, pembrolizumab PSD, March 2023 PBAC meeting). However, at 30 months (OS cut off) there were only 16 patients at risk in the olaparib arm and 6 in the chemotherapy arm, suggesting that the tails of the KM data are highly uncertain.

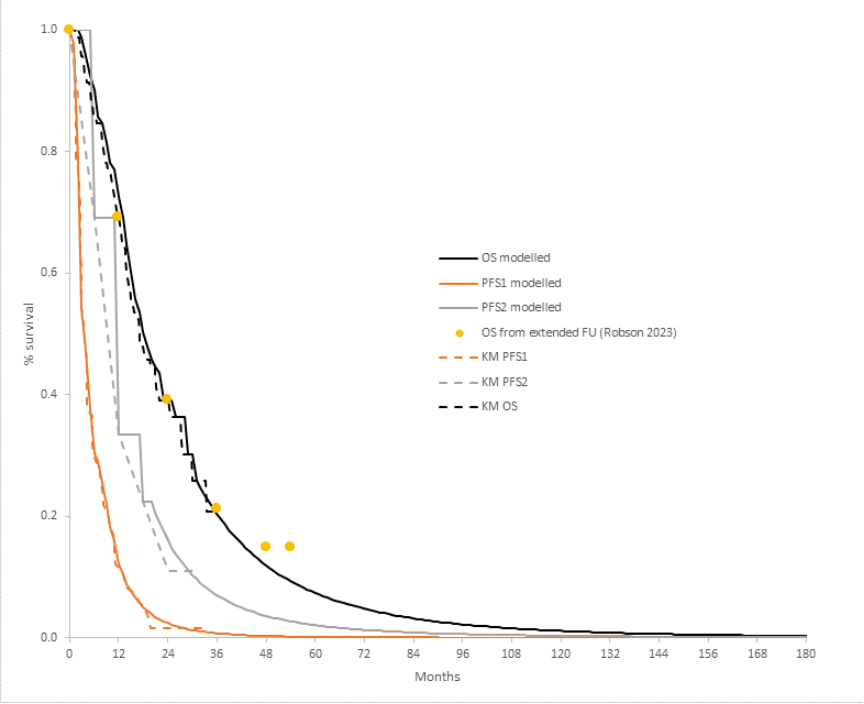
6.51 Figure 5 and Figure 6 present the modelled PFS1, PFS 2 and OS curves from the ITT model for olaparib and chemotherapy, respectively.

Figure 5: Modelled curves for olaparib arm



Source: Figure 3.19, p153 of the submission.
Note: The yellow dot points represent OS data from the extended OS follow-up phase (Robson 2023)

Figure 6: Modelled curves for chemotherapy arm



Source: Figure 3.18, p152 of the submission.
Note: The yellow dot points represent OS data from the extended OS follow-up phase (Robson 2023)

6.52 The submission considered that the data from the final OS analysis was a reasonably good fit to the extended overall survival data for OlympiAD presented in Robson 2023. The commentary noted that the Robson 2023 data only shows noticeably greater survival at the tails of the distributions, and that the modelled OS was lower for both olaparib and chemotherapy. Neither the final nor extended OS DCO showed any statistically significant improvement in overall survival. The PSCR argued that while the OS gain was not statistically significant, a divergence in OS did occur during the trial and the lack of statistical significance could be contributed to the use of effective subsequent anti-cancer therapies in the chemotherapy arm. The ESC agreed with the commentary that, given the lack of statistically significant different OS from the trial data, it was inappropriate for the ITT model to include any OS differences. The pre-PBAC response noted that the PBAC accepted the modelling of an OS gain (HR = 0.9) for olaparib in HR+ patients with eBC despite a lack of statistical significance. In the revised base case presented in the pre-PBAC response, the OS curve for olaparib was estimated by applying the trial-based HR (0.9) from OlympiAD to the OS curve for chemotherapy.

6.53 The submission derived utility weights for patients in the PFS1 and PFS2 health states from the OlympiAD study. The submission sourced the utility weight for the PD health state from the published literature. The submission mapped EORTC QLQ-C30 scores from OlympiAD (Final PFS DCO) to EQ-5D-5L utility values using a mapping algorithm developed by Meunier 2022 (using Australian tariffs reported by Norman 2013). The

ESC advised that the values should have been updated using the most recent Australian value set (Norman 2023)[7].

6.54 The submission noted higher utility scores in the olaparib arm compared to the chemotherapy arm. The submission considered this difference existed for two reasons:

- Firstly, olaparib induced a significantly larger 'disease control rate' than chemotherapy (79.5% versus 47.4%). Thus, olaparib patients are likely to experience fewer disease-related symptoms than chemotherapy patients.
    - The commentary considered this may not be reasonable, as all 'progression free' patients should not be experiencing disease related symptoms (if any) and should have the same HRQoL. The difference in disease control rate would be reflected in the difference in proportion of patients in the progression free and post progression health state instead of a difference between treatments in the same health state.
- Secondly, the higher utility score observed for olaparib is consistent with the safety profiles of olaparib and chemotherapy observed in the OlympiAD trial. Whilst the incidence of 'any adverse event' was similar between the two treatment arms (98% for olaparib versus 96% for chemotherapy), olaparib patients experienced significantly fewer grade 3/4 adverse events than patients treated with chemotherapy (38% versus 49.5%). Furthermore, olaparib patients experienced significantly fewer grade 3/4 adverse events considered causally related to study medication than patients treated with chemotherapy (24% versus 34%).
    - The commentary noted this was inconsistent with the submission's clinical claim of non-inferior safety. It may also be unreasonable to assume that there would be a lower utility for the chemotherapy arm for the entirety of the time spent in PFS1 (0.539 years or 6.47 months) when the mean duration of chemotherapy treatment assumed was only 21.3 weeks of eribulin and vinorelbine (7.1 × three weekly cycles) or 4.9 months of capecitabine.

6.55 The submission did not explain why there would be any differences in PFS2 utilities since olaparib and chemotherapy would have been ceased already. The ESC considered that the application of differential utilities for PFS2 in the submission's model was not justified. The pre-PBAC response acknowledged that PFS2 utility is more likely to be consistent between the treatment arms and applied the pooled utility value for both arms in the pre-PBAC response revised base case.

[7] Norman R, Mulhern B, Lancsar E, Lorgelly P, Ratcliffe J, Street D, Viney R. The Use of a Discrete Choice Experiment Including Both Duration and Dead for the Development of an EQ-5D-5L Value Set for Australia. Pharmacoeconomics. 2023 Apr;41(4):427-438. doi: 10.1007/s40273-023-01243-0. Epub 2023 Jan 31. PMID: 36720793; PMCID: PMC10020301.

6.56 The PSCR argued that differential utilities for PFS (0.746 and 0.662) were accepted in the PBAC's consideration of sacituzumab govitecan (paragraph 7.14 sacituzumab govitecan PSD, March 2022 PBAC meeting) and a similar approach should be applied to the olaparib model. The ESC recalled its advice that a more appropriate base case for the sacituzumab govitecan model would incorporate pooled utilities for the progression free health state (paragraph 6.65, sacituzumab govitecan PSD, March 2022 PBAC meeting). The ESC noted there were additional contextual differences between the submissions that would have a bearing on the PBAC's consideration of the acceptability of differential utility values, including a demonstrated OS benefit. The ESC noted that there was substantial variation in QoL scores from OlympiAD, based on the standard deviation (0.31 for PFS1 in the chemotherapy arm). The ESC noted that the difference in utility values between the treatment arms was substantial, and not consistent with the relatively minor differences in safety. Therefore, the ESC considered the application of differential utilities for PFS1 in the submission's model was not justified and favoured olaparib. The pre-PBAC response maintained that differential utilities were reasonable and consistent with the safety claim for olaparib and the acceptance of differential utilities for sacituzumab govitecan. The pre-PBAC response revised model maintained differential utility values in the PFS health state.

6.57 The model assumed that patients experiencing progression receive a mix of therapies including chemotherapy, CDK4 inhibitors and endocrine therapy. Treatments received in the PFS2 health state were based on post-progression treatments administered in the OlympiAD trial. Subsequent anti-cancer therapy costs were applied as a one off cost associated with transitioning form PFS1 to PFS2. The subsequent treatments were estimated from the whole trial population at the final OS DCO only. Given the extended survival estimated in the subgroup compared to the whole trial, it was unclear to what extent the whole trial subsequent therapy estimates would be reflective of the subgroup population.

6.58 Both the treatments costed and their proportions of use may not accurately reflect the current clinical setting. Specifically, international guidelines (Curgliano 2023) do not recommend CDK4/6 inhibitors after progression from CDK4/6 inhibitors in HR+ HER2-negative patients, and these treatments are not appropriate for TNBC patients. Palbociclib may also not be an informative proxy for subsequent targeted therapies.

6.59 The submission noted that sacituzumab govitecan was not available at the time of the trial, and thus the OlympiAD data was adjusted to assume that 50% of eligible TNBC patients would receive post progression sacituzumab govitecan. However the submission applied only the costs and not the benefits associated with sacituzumab govitecan, which favoured olaparib. The ESC agreed with the commentary this was not appropriate, and considered that the post-progression treatment costs should reflect the treatments received in the trial, consistent with the modelled treatment benefit. The subsequent treatment costs in the base case assumed the same

proportion of use of SG in both arms of the model and therefore removal of costs for SG had only a very small impact on the ICER.

6.60 The submission derived the cost of terminal care from Reeve 2018. The submission considered that this was consistent with the value approved by the PBAC during the evaluation of olaparib in the early breast cancer setting. The cost of palliation in the model is $27,107 applied as a one off cost at the time of death. The PBAC, in its consideration of pembrolizumab plus chemotherapy for TNBC, had considered Reeve to overestimate terminal care, and had accepted a revised terminal care cost of $6,050 (Pembrolizumab PSD, March 2023 PBAC meeting). However inclusion of terminal care costs was not a key driver of the olaparib model.

6.61 The submission's approach to estimating *BRCA* testing costs did not account for the prevalence of *BRCA*m, and therefore the number needed to test to identify one patient eligible for treatment. As such, the ESC considered that *BRCA* testing costs were underestimated in the model. Based on the submission's assumption of 5% and 13.25% *BRCA*m prevalence in HR+ mBC and TNBC, respectively, the number of tests required for one patient to be classified as *BRCA*m (and eligible for olaparib) would be 20 and 7.5, respectively. For comparison, the economic model estimated an additional 0.17 (0.26 tests for olaparib and 0.09 tests for chemotherapy) *BRCA* tests per olaparib patient treated. Accounting for the number of tests required to identify one *BRCA*m patient and removing *BRCA* testing costs from the comparator, the ICER increased by % in the ITT model. The PBAC considered it was appropriate for the testing costs in the model to account for the total additional *BRCA* testing costs, including accounting for the number of tests needed to identify one patient classified as g*BRCA*m.

6.62 The PSCR stated that in the November 2023 PBAC submission for olaparib in eBC, *BRCA* testing costs assumed 74% of TNBC and 20% of HR patients would already receive *BRCA* testing consistent with Australian clinical practice and a similar approach was taken in the mBC submission. The PSCR also noted that once olaparib is available in the eBC setting, the vast majority of patients who progress from eBC to mBC will already be aware of their germline *BRCA* status upon metastatic recurrence. The pre-PBAC response argued that additional testing costs were not appropriate due to the substantial testing that occurs in clinical practice. The base case economic model already accounts for testing in earlier settings and assumes that only 10% of patients progressed from eBC and 95% of de novo mBC patients would require *BRCA* testing. This is appropriate, and was maintained in sensitivity analyses (Table 14).

6.63 The commentary noted the financial estimates assumed a higher proportion of de novo patients than in the model. In the financial estimates 20.5% of TNBC patients were assumed to be de novo mBC and 34% of HR+ patients were assumed to be de novo, compared with 18% overall (in OlympiAD). The assumption of a higher proportion of de novo patients increased the testing costs slightly as these patients would not have been tested in the eBC setting.

6.64 Table 12 presents a summary of the key drivers of the model. In the subgroup model, the only key drivers were efficacy inputs such as OS extrapolation and PFS2 health state assumptions. However as the OS benefit assumed in the no prior chemotherapy subgroup may not be supported, the entire model should be considered uncertain and may not be informative.

Table 12: Key drivers of the model

Description	Method/Value	Impact
ITT model		**Base case: $[redacted][1]/ QALY gained**
OS improvement assumption	The submission extrapolated ITT OS KM data from OlympiAD, which assumed a survival increment associated with olaparib despite no statistically significant difference being demonstrated in the trial.	High, favours olaparib. Applying the olaparib OS curve to the chemotherapy arm increases the ICER by [redacted]% to $[redacted][2]
PFS2 extrapolation	The submission extrapolated PFS2 using a generalized gamma function.	High, favours olaparib Use of a lognormal function increases the ICER by [redacted]% to $[redacted][2]
Differential Utilities	The submission assumed different utilities for olaparib and chemotherapy in both PFS1 (0.817 vs 0.745) and PFS2 (0.749 vs 0.717) health states.	Assuming no differential utilities increased the ICER by [redacted]% to $[redacted][2]/QALY

Source: Submission's attached economic model spreadsheet
ICER = incremental cost-effectiveness ratio; ITT = intention to treat; OS = overall survival; PFS2 = time to second progression to death; PD = progressed disease; QALY = Quality adjusted life-year;
The redacted values correspond to the following ranges:
[1] *$75,000 to < $95,000*
[2] *$95,000 to < $115,000*

6.65 Table 13 presents the results of the ITT model. The submission did not present a stepped economic evaluation for the ITT model.

Table 13: Results of the economic evaluation in the ITT model

Component	Olaparib	Chemotherapy	Increment
Costs	$[redacted]	$65,260	$[redacted]
LYG	2.18	1.91	0.267
Incremental cost/extra LYG gained			$[redacted][1]
Costs	$[redacted]	$65,260	$[redacted]
QALY	1.648	1.265	0.383
Incremental cost/extra QALY gained			**$[redacted][2]**

Source: Tables 3.34, p154 of the submission.
LYG = life year gained; QALY = quality adjusted life year
The redacted values correspond to the following ranges:
[1] *$95,000 to < $115,000*
[2] *$75,000 to < $95,000*

6.66 The results of key univariate sensitivity analyses of the ITT model are summarised in Table 14.

Table 14: Results of key sensitivity analyses in the ITT model

Analyses	Incremental cost ($)	Incremental QALY	ICER	% Change
Base case	[redacted]	**0.383**	[redacted][1]	
Discounting rate (5% in BC)				
0%	[redacted]	0.439	[redacted][2]	-[redacted]%
Time horizon (10 years in BC)				
15 years	[redacted]	0.430	[redacted][2]	-[redacted]%

Analyses	Incremental cost ($)	Incremental QALY	ICER	% Change
7 years	[redacted]	0.335	[redacted][1]	[redacted]%
5 years	[redacted]	0.293	[redacted][3]	[redacted]%
PFS extrapolation both arms (lognormal in BC)				
Weibull used to extrapolate PFS	[redacted]	0.378	[redacted][1]	[redacted]%
Exponential used to extrapolate PFS	[redacted]	0.380	[redacted][1]	[redacted]%
Gen Gamma used to extrapolate PFS	[redacted]	0.736	[redacted][4]	-[redacted]%
PFS2 extrapolation both arms (Generalised Gamma in BC)				
Weibull used to extrapolate PFS2	[redacted]	0.304	[redacted][3]	[redacted]%
Exponential used to extrapolate PFS2	[redacted]	0.319	[redacted][3]	[redacted]%
Loglogistic used to extrapolate PFS2	[redacted]	0.316	[redacted][3]	[redacted]%
Gompertz used to extrapolate PFS2	[redacted]	0.303	[redacted][3]	[redacted]%
Lognormal used to extrapolate PFS2	[redacted]	0.312	[redacted][3]	[redacted]%
OS extrapolation both arms (log normal in BC)				
Weibull used to extrapolate OS	[redacted]	0.372	[redacted][1]	[redacted]%
Loglogistic used to extrapolate OS	[redacted]	0.361	[redacted][1]	[redacted]%
Extended OS follow-up (Robson 2023) used to extrapolate OS	[redacted]	0.397	[redacted][1]	-[redacted]%
Utilities				
Removal of treatment-specific utility scores in both PFS1 and PFS2 *#1*	[redacted]	0.311	[redacted][3]	[redacted]%
Removal of treatment-specific utility scores in PFS2 only	[redacted]	0.355	[redacted][1]	[redacted]%
Utility in PFS2 set to same as PD	[redacted]	0.308	[redacted][3]	[redacted]%
Costs				
Account for *BRCA*m prevalence in testing [a]	[redacted]	0.383	[redacted][1]	[redacted]%
BRCA testing rates/costs consistent with proportion of de novo patients in financial estimates, accounting for the number of tests required to identify one *BRCA*m patient and removing *BRCA* testing costs from the comparator [b] #2	[redacted]	0.383	[redacted][1]	[redacted]%
Using time in PFS1 to inform treatment duration (olaparib: 11.85 months, chemotherapy: 8.81cycles/6.08 months)	[redacted]	0.282	[redacted][1]	[redacted]%
Post progression targeted therapy use set to 0%	[redacted]	0.383	[redacted][1]	[redacted]%
Removal of sacituzumab govitecan from post-progression costs #3	[redacted]	0.383	[redacted][1]	<[redacted]%
Olaparib DPMQ $2,581.31 ($1,209.59 AEMP, price in eBC) #5	[redacted]	0.383	[redacted][4]	-[redacted]%
OS (based on extrapolated KM curves in BC)				
OS in chemotherapy set equal to OS in Olaparib arm [c] *#4*	[redacted]	0.241	[redacted][3]	[redacted]%
OS for olaparib estimated by applying the trial-based HR (0.9) to the chemotherapy OS curve (as per pre-PBAC response).	[redacted]	0.334	[redacted][1]	[redacted]%
Multivariate Sensitivity analyses (conducted for ESC) – corrected				
#1 and #2	[redacted]	0.311	[redacted][3]	[redacted]%
#1, #2 and #3	[redacted]	0.311	[redacted][3]	[redacted]%
#1, #2, #3 and #4	[redacted]	0.169	[redacted][5]	[redacted]%
#1, #2, #3, #4 and #5	[redacted]	0.169	[redacted][3]	[redacted]%

Source: Calculated during the evaluation using the submission's economic model.

BC = base case; DCO = data cutoff; eBC = early breast cancer; ICER = incremental cost effectiveness ratio; OS = overall survival; PD = progressed disease PFS1 = progression free survival 1: PFS2 = progression free survival 2; QALY = quality adjusted life year

[a] Assuming 5% prevalence (20 tests per patient treated) for HR+ mBC and 13.25% prevalence (7.5 tests per patient treated) for TNBC, and 13 tests (weighted prevalence based on 8% HR+ mBC and 10% TNBC as assumed for de novo mBC patients) for patients who progressed from eBC.

[b] Assuming 20.5% HR+ patients de novo and 34.0% TNBC patients de novo (consistent with financial estimates), assumes 95% of de novo patients receive testing and 10% of patients progressed from eBC receive testing. Accounting for *BRCA*m prevalence (5% de novo HR+, 13.25% de novo TNBC and 9.6% eBC (weighted)), 3.82 patients would be tested to identify one patient for olaparib treatment.
[c] calculated during the evaluation by pasting values from Column H of 'olaparib trace' to Column H of 'chemo trace'.
The redacted values correspond to the following ranges:
[1] *$75,000 to < $95,000*
[2] *$55,000 to < $75,000*
[3] *$95,000 to < $115,000*
[4] *$35,000 to < $45,000*
[5] *$155,000 to < $255,000*

6.67 Overall, the ITT model was highly sensitive to the choice of extrapolation of PFS2. Though the Generalised gamma extrapolation was the best fitting by total AIC and BIC score, the others were also well fitting and the generalised gamma extrapolation reported the most optimistic ICER. Additionally, the model was sensitive to the utility in PFS2 and setting disease monitoring costs in PFS2 equal to PD, suggesting that the modelling of benefit associated with PFS2 may be uncertain and overestimated. Using time in PFS1 to inform treatment duration also increased the ICER by [redacted]%. Assuming OS in the chemotherapy arm to be the same as that in the olaparib arm, consistent with the lack of statistically significant improvement in the OlympiAD trial, increased the ICER by [redacted]%.

6.68 Overall, the commentary considered the ITT model's ICER appeared underestimated and may be optimistic, particularly because an OS benefit was modelled even though it was not reported in OlympiAD, and differential utilities by treatment arm were applied.

6.69 The ESC considered that a respecified base case using the ITT model should be considered, applying the following changes to model inputs:

- Non treatment-specific utility values for each PFS1 and PSF2 health states (see paragraph 6.53-6.56)
- *BRCA* testing rates/costs consistent with approach in financial estimates (accounting for the number of tests required to identify one *BRCA*m patient and removing *BRCA* testing costs from the comparator) (see paragraph 6.61).
- Removal of costs for subsequent use of sacituzumab govitecan (see paragraph 6.59)
- No difference in OS rates (OS in chemotherapy set equal to OS in olaparib) (see paragraph 6.52).

The ESC noted that these changes increased the ICER by [redacted]%, from $75,000 to < $95,000 to $155,000 to < $255,000[8] per QALY.

6.70 The pre-PBAC response argued that while there was no statistically significant difference in OS, there was a clear separation of OS curves in the trial and attributed

[8] Revised to correct removal of sacituzumab govitecan costs

the lack of statistical difference in OS to the use of subsequent anti-cancer treatments. The PBAC acknowledged the challenge of demonstrating OS benefit in this setting and the limitations of the trial, which was not powered to detect a difference in OS. The PBAC considered that although OS in the base case model was likely to be overestimated, it was reasonable for the model to assume some difference in survival given the PFS1 and PFS2 benefit, the divergence in OS curves which was maintained in the longer follow-up data, and because OS in the trial was likely to be impacted by subsequent treatments not available in Australian clinical practice.

6.71 The PBAC noted that the pre-PBAC response proposed a revised base case, applying the following changes to the ITT model:

- A revised DPMQ ($).
- *BRCA* testing costs assuming a higher proportion of de novo patients (20.5% of TNBC and 34% of HR+).
- Pooled utility value for both arms for PFS2 (differential utility values maintained for PFS1).
- OS curve for olaparib estimated by applying the trial-based HR (0.9) to the OS curve for chemotherapy.
- Updated PBS mark-ups and MBS unit costs as at 1 July 2024.

The pre-PBAC response stated that this resulted in an ICER or $45,000 to < $55,000 per QALY (or $45,000 to < $55,000 per QALY using the Robson 2023 extended follow-up data).

6.72 The PBAC considered ESC's respecified base case was appropriately conservative, given the uncertainty in the PFS and OS benefit for olaparib, especially as the trial comparator does not fully represent standard of care. However, although a statistically significant difference in OS was not demonstrated in the trial the PBAC considered a survival benefit was plausible as a trend to improved OS was shown in the trial. The PBAC noted that when the pre-PBAC price and pre-PBAC approach to modelling OS was applied to the ESC respecified base case (as per paragraph 6.69) the ICER was reduced to $75,000 to < $95,000 per QALY.

Drug cost/patient/course

6.73 Table 15 presents the cost per patient for olaparib and chemotherapy at the revised price from the pre-PBAC response.

Table 15: Drug cost per patient for olaparib and chemotherapy (whole trial)

	olaparib Trial dose and duration	olaparib Model	olaparib Financial estimates	chemotherapy Trial dose and duration	chemotherapy Model	chemotherapy Financial estimates
Mean dose	NR[a]	600mg		NR	Capecitabine: 4,500mg/day Eribulin: 2.52mg/ infusion Vinorelbine: 54mg/ infusion	Cost offsets not included
Mean duration	10 months			4.9 months		
Cost/patient/month	$[b]			$1,188.38[c]		
Cost/patient/course	$			$5,823.06[d]		

Source: Attached economic evaluation and attached financial model.

[a] Mean dose was not reported for the subgroup population. This would have no impact on costs as both 100mg and 150mgs have the same requested price.

[b] Based on a prorated effective DPMQ for 28 days of $[redacted].

[c] prorated from total cost per course

[d] Based 7.1 21 days cycle (equating to 4.9 months) of Eribulin costed at $12,040.24, vinorelbine costed at $3,998.85, and 4.9 months of capecitabine costed at $549.96, with proportional use of 37.36%, 17.58% and 45.05%, respectively.

6.74 A mean cost per course of olaparib was estimated at $[redacted] based on a DPMQ of $ for 28 days of treatment and 10 months treatment duration in the whole trial population. A mean cost per course of the weighted chemotherapy comparator was estimated as $5,823.06 based on 4.9 months of treatment.

Estimated PBS usage & financial implications

6.75 This submission was not considered by DUSC. The submission took an epidemiological approach to estimating use and financial implications. The pre-PBAC response noted that the financial estimates provided in the submission were based on the 'no prior chemotherapy' subgroup. The PBAC considered it would be appropriate for the estimates to be amended to reflect the broader population, including patients with HER2-negative mBC with a confirmed *BRCA* mutation, who have received chemotherapy in the adjuvant/neoadjuvant or metastatic setting.

6.76 Table 16 presents the key inputs relied on in the financial estimates.

Table 16: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
% of patients with recurrent mBC	66%	Average of Kisqali Access Registry for Metastatic Breast Cancer in Australia (KARMA, n=160) registry and ARORA registry.	The ARORA registry considered that 59% of HR+ patients had relapsed as opposed to de novo metastatic disease and the KARMA registry considered that 74% would have relapsed or recurrent disease.
% of HR + patients with prior (neo)adjuvant chemotherapy	63%	Taken from KARMA registry	The PBAC previously considered that 25% would be more appropriate. (Table 19, olaparib PSD, November 2023 PBAC meeting). The pre-PBAC response clarified that this was the proportion of patients meeting PBS criteria for high risk of disease recurrence. The pre-PBAC considered this should be increased to 95% to reflect the broader population to include patients with prior chemotherapy in any setting.

Data	Value	Source	Comment
Germline *BRCA* mutation testing rates	TNBC: 75-90% HR+: 50-90%	Olaparib March 2023 PSD Table 20	In the eBC setting, DUSC had considered rates ranging from 80% to 95% to be appropriate, but that initially uptake may be higher. It was unclear how applicable uptake rates from the eBC setting would be to the metastatic setting.
Germline *BRCA* mutation test positive to *BRCA1* or *BRCA2* mutation, TNBC	13.25%	Olaparib March 2023 PSD Table 20	Consistent with previous consideration.
Germline *BRCA* mutation test positive to *BRCA1* or *BRCA2* mutation, HR+	5%	Assumption to align with in the OlympiA trial, estimates from population based studies (Armstrong 2019) and IPSOS report, showing that testing is less established in this population	This was consistent with previous MSAC considerations (Table 1and 6, 1716 PSD November 2023 MSAC meeting).
Proportion of TNBC patients	15%	Sacituzumab Govitecan March 2022 PSD Table 6.70	Reasonable. This was consistent with DUSC recommendations in the sacituzumab govitecan November 2021 PSD.
Estimate of TNBC patients that are metastatic	54.80%	Trastuzumab deruxtecan November 2023 PSD Table 16	In its consideration of trastuzumab deruxtecan at the July 2022 PBAC meeting DUSC had stated: "DUSC agrees with the commentary that this is likely an overestimate. However, DUSC noted that this employs similar rationale to other submissions (atezolizumab March 2020 and SG for triple negative breast cancer). In prior submissions, for atezolizumab March 2020 and pembrolizumab March 2023, this has also taken into account the mortality rate of (44% for all stages of breast cancer from Lin 2012[e]) into the estimates" (Table 14, trastuzumab deruxtecan PSD, November 2023 PBAC meeting)
Proportion of de novo / recurrent patients in HER2-/HR+	34%	Average of ARORA registry and Karma Registry average	Substantially greater than the 12.6% de novo patients in the OlympiAD trial.
Proportion of de novo TNBC patients	20.5%	Midpoint of North Carolina mBC registry (File 2022) and PRAEGNANT (Muller 2022), a German prospective breast cancer registry to assess treatment patterns and quality of life and to identify patients who may be eligible for clinical trials or specific targeted treatments.	It was unclear to what extent these estimates would be applicable to the Australian setting. In the sacituzumab govitecan November 2021 PSD (Table 15), 34.8% of TNBC patients were assumed to be diagnosed with unresectable locally advanced or de novo metastatic TNBC. In the KN-355 trial, which was considered by the PBAC at the March 2023 PBAC meeting, there was 30% de novo metastatic TNBC patients. (paragraph 6.6, pembrolizumab PSD, March 2023 PBAC meeting).
Treatment utilisation			
Average duration of olaparib treatment	13 months (de novo), 12 months (recurrent)	Submission economic evaluation	This was consistent with the economic evaluation for the no prior chemotherapy subgroup (mean duration of treatment of 12.3 months). However, for the ITT population the duration of treatment is likely to be shorter (10 months in the economic model).

Data	Value	Source	Comment
Cost of germline *BRCA1* or *BRCA2* mutation testing	$1,200	MBS item 73295	Consistent with existing MBS item

Source: Tables 4.1, p157 of the submission.

AIHW = Australian Institute for Health and Wellness; CDK = cyclin-dependent kinase; DPMQ = dispensed price per maximum quantity; DUSC = Drug utilisation Sub Committee; eBC = early breast cancer; HER2 = Human epidermal growth factor receptor; HR + = hormone receptor positive; mBC = metastatic breast cancer; MBS = Medicare benefits schedule; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; TNBC = triple negative breast cancer;

6.77 Table 17 presents the estimated number of patients eligible for olaparib, which ranged from < 500 in Year 1 to < 500 in Year 6. The submission assumed that 100% of eligible patients would receive treatment with olaparib.

Table 17: Estimated number of TNBC and HR+ HER2-negative patients eligible for olaparib

	2025	2026	2027	2028	2029	2030
TNBC patients						
Incident population	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Triple negative patients (15%)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Metastatic/ unresectable (54.8%)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Recurrent population (79.5%)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Proportion tested for *BRCA*	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Recurrent population tested for *BRCA*	[redacted][2]	[redacted][b2]	[redacted][2]	[redacted][2]	[redacted][c2]	[redacted][2]
Recurrent *BRCA*m (13.25%)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
De Novo Metastatic breast cancer (20.5%)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Proportion tested for *BRCA*	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
De novo population tested for *BRCA*	[redacted][a3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
De novo *BRCA*m (13.25%)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total eligible TNBC patients	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
HR+ HER2-negative patients						
Incident population (CDK 4/6 inhibitor population)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Recurrent population (66%)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Proportion tested for *BRCA*	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Recurrent metastatic cancer tested for *BRCA*	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Recurrent metastatic cancer who have received (neo)adjuvant chemotherapy (63%), and tested for *BRCA*	[redacted][3]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Recurrent metastatic cancer who have received (neo)adjuvant chemotherapy, and *BRCA*m (5%)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
De Novo Metastatic breast cancer (34%)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Proportion tested for *BRCA*	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
De novo population tested for *BRCA*	[redacted][3]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
De novo *BRCA*m (5%)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total eligible HR+ HER2-negative patients	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total patients eligible for olaparib	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]

Source: Tables 4.2-4.10, pp159-164 of the submission, Table 4.22 and 4.23, pp171-172 of the submission and attached financial spreadsheet.

HER2-negative = human epidermal growth factor receptor negative; HR + = hormone receptor positive; TNBC = triple negative breast cancer

[a] The submission presented an estimate of <500 which was inconsistent with estimates in the financial spreadsheet and testing considerations in Section 4.5.

[b] The submission presented an estimate of 500 to < 5,000 which was inconsistent with estimates in the financial spreadsheet and testing considerations in Section 4.5.

[c] The submission presented an estimate of 500 to < 5,000 which was inconsistent with estimates in the financial spreadsheet and testing considerations in Section 4.5.

The redacted values correspond to the following ranges:

[1] *20,000 to < 30,000*

[2] *500 to < 5,000*

[3] *< 500*

6.78 Table 18 presents the estimated number of new *BRCA* tests required as a result of the proposed listing, which ranged from 500 to < 5,000 in Year 1 to 500 to < 5,000 in Year 6. The submission estimated that an increasing proportion of recurrent patients would already know their *BRCA* status from testing in eBC, and would not require

testing after diagnosis of mBC. The ESC considered this was reasonable. For the TNBC population, the submission stated that recurrence from eBC usually occurs within the first three years (Soares 2021) and estimated that an increasing proportion of the recurrent TNBC population would already know their *BRCA* status at diagnosis of mBC (from [redacted]% in Year 1 to [redacted]% in Years 5 and 6). This reduced the estimated number of new *BRCA* tests by up to 500 to < 5,000 tests per year (Table 18). For the HER2-negative/HR+ population, the submission stated that recurrence from eBC for patients with a known *BRCA* status was not expected within the 6-year time horizon, given HER2-/HR+ patients commonly have recurrence after 5 years and will spend approximately 2 years on CDK4/6 inhibitors. Therefore, the submission assumed a declining rate of new *BRCA* tests performed after mBC diagnosis in the TNBC population (proportion decreases from [redacted]% in Year 1 to [redacted]% in Years 5 and 6), but not for the HER2-/HR+ population (proportion increases from [redacted]% in Year 1 to [redacted]% testing in mBC from Year 4 onwards). Unlike the economic model, the financial estimates accounted for the number needed to test to identify one patient eligible for treatment (e.g. in year 6 there were 500 to < 5,000 estimated *BRCA* tests and < 500 patients initiating treatment with olaparib).

Table 18: Total uptake of *BRCA* tests

	2025	2026	2027	2028	2029	2030
TNBC Patients						
De novo TNBC taking up *BRCA* testing	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Recurrent TNBC taking up *BRCA* testing	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Total TNBC patients taking up *BRCA* testing	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Proportion of recurrent TNBC who know their *BRCA* status due to eBC testing	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Estimated patients who know their status from testing in eBC	[redacted]1	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Estimated recurrent patients who take up testing in mBC	[redacted]2	[redacted]2	[redacted]2	[redacted]1	[redacted]1	[redacted]1
Total TNBC patients requiring test in mBC	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]1	[redacted]1
HR+ HER2-negative patients						
De novo HR+ patients taking up *BRCA* testing	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Recurrent HR+ patients taking up *BRCA* testing	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Total number of HR+ patients taking up *BRCA* testing	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Total new *BRCA* tests	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
De novo patients only	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2

Source: Table 4.22 and 4.23, pp171-172 of the submission and attached financial spreadsheet.
HR+ = hormone receptor positive; TNBC = triple negative breast cancer
The redacted values correspond to the following ranges:
[1] < 500
[2] 500 to < 5,000

6.79 The submission assumed a test cost of $1,200 based on Item 73295 for germline *BRCA* mutation test and applied an MBS rebate of 80%.

6.80 Table 19 presents the estimated use and financial implications in the submission. During the evaluation, two errors were identified. First, the submission financial spreadsheet assumed no usage of olaparib in HR+ de novo patients. Second, Cell H111 of the 2d. Patients DTG worksheet included the word “remove” instead of the

appropriate number [3] in the cell. Both of these errors were addressed and corrected results are presented below.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of olaparib						
TNBC patients						
Recurrent	1	1	1	1	1	1
De novo	1	1	1	1	1	1
Total treated TNBC patients	1	1	1	1	1	1
HR+						
Recurrent metastatic cancer who received (neo)adjuvant chemotherapy	1	1	1	1	1	1
De novo	1	1	1	1	1	1
Total treated HR+ HER2-negative patients	1	1	1	1	1	1
Total olaparib prescriptions[a]	2	2	2	2	2	2
Recurrent scripts only	2	2	2	2	2	2
De novo scripts only	2	2	2	2	2	2
Net financial implications						
Net cost to PBS/RPBS	3	3	3	3	3	3
Total costs to the MBS for *BRCA* testing	4	4	4b	4	4	4
Total costs to Government	3	3	3	3	3	3
Net financial implications pre-PBAC response revised						
Net cost to PBS/RPBS	3	3	3	3	3	3
Total costs to the MBS for *BRCA* testing	4	4	4	4	4	4
Total costs to Government	3	3	3	3	3	3

Source: Table 4.17, p169 of the submission and the attached financial model, corrected
PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
[a] assumes 13.3 scripts per patient per year
The redacted values correspond to the following ranges:
[1] < 500
[2] 500 to < 5,000
[3] $10 million to < $20 million
[4] $0 to < $10 million

6.81 In the submission, the total cost to the PBS/RPBS of listing olaparib was estimated to be $10 million to < $20 million in Year 1, increasing to $10 million to < $20 million in Year 6, and a total of $90 million to < $100 million in the first 6 years of listing. With pre-PBAC revisions to the patient numbers (to include patients who have received chemotherapy in the metastatic setting) and the price ($ DPMQ), the total cost to the PBS/RPBS was revised to $0 to < $10 million in year 1, increasing to $10 million to < $20 million in year 6.

6.82 The submission assumed < 500 grandfathered patients based on an access program. These patients were added to the incident population in Year 1 of listing. This was reasonable.

6.83 The financial estimates presented may be uncertain as:

- The number of packs of olaparib used may be underestimated as the duration of treatment of olaparib (based on mean usage in OlympiAD) may be underestimated as assessment for progression in clinical practice may be less frequent than in clinical trials therefore patients were less likely to discontinue precisely at progression. The PBAC considered this is unlikely to have a substantial impact on the duration of treatment. The PBAC noted that the duration of treatment in the submission base case was based in the 'no prior chemotherapy' subgroup (12.3 months in the economic model), however this is likely to be shorter for the more relevant ITT population (10 months in the economic model). The PBAC considered the financial estimates should be revised to reflect the expected duration of treatment for the ITT population.
- The submission estimates assumed that all de novo patients would be eligible for treatment, however the PBAC considered that patients should be required to have received chemotherapy prior to olaparib. This may overestimate the number of de novo patients treated with olaparib if some patients do not receive a second line of treatment in the metastatic setting. However, the PBAC considered that the proportion would be very small (no more than 5%) and it was not necessary to adjust the estimates for this circumstance.
- The submission did not calculate cost offsets for treatments replaced, which may overestimate total net costs. The ESC considered that olaparib is unlikely to replace other costly targeted therapies such as CDK4/6 inhibitors or pembrolizumab. The ESC considered that olaparib would only replace sacituzumab govitecan in patients where it is unable to be used sequentially.

6.84 The proportion of de novo mBC patients was uncertain. The OlympiAD trial (12.6%) reported a lower proportion of de novo patients than the KARMA registry (26%) or ARORA registry (41%). In the base case of the financial estimates the submission used the average of KARMA and AURORA (34%) to estimate the number of de novo HR+ patients. Similarly, the proportion of de novo metastatic TNBC patients assumed (20.5%, based on File 2022, a US registry and Muller 2022, a German registry), was lower than what was previously considered by the PBAC for sacituzumab govitecan (34.8%, Table 15, sacituzumab govitecan PSD, November 2021 PBAC meeting) and for pembrolizumab (30% as enrolled in KN355, paragraph 6.6, pembrolizumab PSD, March 2023 PBAC meeting). Should the proportion of patients with de novo disease be lower than expected then the number of *BRCA* tests may be overestimated, and vice versa.

Quality Use of Medicines

6.85 The submission stated that activities initiated (current and future) by AstraZeneca to promote and support quality use of medicines are based on educational and training programs to prescribers and patients.

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

Financial Management – Risk Sharing Arrangements

6.87 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 mBC that recognises the value of this treatment and shares the risk of uncertainty between the Sponsor and the Department. However no specific arrangements were proposed.

6.88 In November 2023, when recommending olaparib for listing in high risk eBC, the PBAC advised that a Risk Sharing Arrangement (RSA) should be implemented given uncertainty with patient numbers and testing/treatment uptake (paragraphs 7.10 to 7.11 olaparib PSD, November 2023 PBAC meeting). The PBAC considered it would be appropriate for financial caps for the RSA for eBC to be increased to account for additional use in patients with mBC.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of olaparib for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer and a confirmed *BRCA1* or *BRCA2* pathogenic variant. The PBAC is satisfied that olaparib provides, for some patients, a significant improvement in efficacy compared with chemotherapy in terms of progression free survival. Although a statistically significant difference in OS was not demonstrated in the trial, the PBAC considered a survival benefit was plausible as there was a trend to improved OS in the trial and increased subsequent use of PARP inhibitors in the control arm. The PBAC noted that olaparib is PBS-listed for patients with high-risk early breast cancer (eBC), but considered there remains a clinical need for access to olaparib for patients not eligible in the early setting, particularly lower risk patients who have progressed to metastatic disease and patients diagnosed with de-novo metastatic disease. The PBAC considered the incremental cost-effectiveness ratio remained high at the price proposed in the pre-PBAC response and a price reduction would be required to bring the ICER into an acceptable range. The PBAC considered some changes to the financial estimates were required to align them with the revised patient population for the listing. Given the uncertainty in patient numbers, uptake and duration of treatment, the PBAC considered a risk sharing arrangement would be appropriate.

7.2 The PBAC recalled that olaparib was recommended for patients with HER2-negative *BRCA*m breast cancer in the high risk eBC setting in November 2023 and the Committee had previously noted that patients with de novo metastatic disease would not be able to access olaparib under the proposed listing, but that cost-effectiveness

had not been assessed in this population. The PBAC noted that the submission had proposed that the clinical place for olaparib was in patients with HER2-negative, *BRCA*m mBC who have not received chemotherapy in the metastatic setting, arguing that this represents the patient population that derives the greatest treatment benefit from olaparib based on subgroup results from the pivotal trial (OlympiAD). However, in line with the ESC advice, the pre-PBAC response proposed to revise the positioning of olaparib to include all HER2-negative, *BRCA*m mBC patients who have received prior chemotherapy (in either the early or metastatic setting), recognising the unmet clinical need in the broader patient population. The PBAC considered it was appropriate for the clinical place of olaparib to include treatment of: (1) patients progressing to mBC after adjuvant/neoadjuvant treatment with chemotherapy in the eBC setting, and (2) patients who have been treated with chemotherapy in the metastatic setting (progressed from eBC or de novo), consistent with the OlympiAD trial population and the TGA indication for olaparib in mBC.

7.3 For the olaparib restrictions in mBC the PBAC considered five repeats for continuing treatment would be appropriate, as treatment would be continued until disease progression. The PBAC considered an Authority Required (telephone/online PBS Authorities system) would be appropriate for the Continuing treatment phase, consistent with the listing in eBC. The PBAC considered that the restrictions should require patients to have received prior chemotherapy, either in the adjuvant/neoadjuvant setting, or in the metastatic setting, consistent with the trial population and TGA indication. The proposed restriction did not prevent use of olaparib following pembrolizumab plus chemotherapy in patients with TNBC and combined positive score (CPS) ≥10. Although no evidence for use of olaparib in this population was provided in the submission as the trial was conducted prior to availability of pembrolizumab for mBC, the PBAC considered it was reasonable for the restrictions to not exclude patients with prior treatment with pembrolizumab as it is unlikely to impact on treatment outcomes for olaparib. The PBAC considered it would not be appropriate for patients to receive retreatment with olaparib after use in the eBC setting in the absence of supporting evidence. The PBAC noted there is no need for a separate grandfather restriction as patients will be eligible under the initial restriction.

7.4 The PBAC considered it was reasonable for the mBC listing to be consistent with the eBC listing with respect to *BRCA* testing, without specifying that the *BRCA* mutation is germline (rather than somatic). The PBAC noted advice from the Secretariat that "variant" is the preferred terminology and considered it would be appropriate the criterion to include 'pathogenic variant' in place of 'mutation'. The PBAC noted that revision of the MBS item remained for MSAC consideration, but considered that it should align with the PBS restriction population to include patients with de novo mBC as well as those who have progressed to metastatic disease following diagnosis with eBC.

7.5 The submission's nominated comparator was standard of care, which the submission defined as chemotherapy. The PBAC noted that for a proportion of patients relevant comparators would include: 2L endocrine therapy (after CDK 4/6 inhibitors and endocrine therapy) and sacituzumab govitecan (as 3L therapy in de novo TNBC or 2L in recurrent TNBC). In addition, the ESC considered that the chemotherapies included as the standard of care (control) arm in the clinical evidence did not necessarily represent the best choice of regimen for patients with *BRCAm* mBC, which would include a platinum-based chemotherapy. The PBAC considered that standard of care was the appropriate comparator, but that chemotherapy did not reflect current standard of care for all patients.

7.6 The PBAC noted that submission was based on one trial, OlympiAD, an open label randomised controlled trial which compared olaparib (n=205) to chemotherapy (n=97) in patients with confirmed germline *BRCAm* and HER2-negative mBC, who had been previously treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Although the submission had also presented results of the subgroup of patients with no prior chemotherapy in the metastatic setting, the PBAC considered that the ITT population was most relevant to the revised population for listing as per paragraph 7.2. As the OlympiAD trial was conducted between 2014 and 2017, the control arm did not fully reflect current standard of care. The PBAC considered that this is likely to overestimate the benefit for olaparib in current clinical practice.

7.7 The PBAC considered that the OlympiAD trial demonstrated that there was a moderate added benefit for olaparib in terms or PFS, with 2.8 months additional PFS and a 13% absolute reduction in the risk of disease progression or death compared to chemotherapy (12-month PFS 25.9% vs 15%, HR: 0.58; 95% confidence interval [CI] 0.43 to 0.80; p<0.001 December 2016 data cut). The PBAC considered the magnitude of PFS benefit was somewhat uncertain as the comparator treatments are unlikely to fully represent standard of care. The PBAC noted that no significant difference in the median OS was observed between the olaparib and the chemotherapy arms at either data cut off. The submission argued that while there was no statistically significant difference in OS, there was a clear convergence in OS in the trial and OS was impacted by subsequent treatments. The PBAC considered that the data did not clearly support an OS benefit, but acknowledged the challenge of demonstrating OS benefit in this setting due to subsequent treatments and the limitations of the trial, which was not powered to detect a difference in OS.

7.8 The PBAC considered that results in the subgroup of patients with no prior chemotherapy in the metastatic setting were unreliable as they were affected by potential confounding, small sample size and not formally tested for statistical significance. Further, they were not relevant to the broader patient population considered appropriate for listing.

7.9 The PBAC considered the claim of non-inferior safety was generally supported when compared to the three chemotherapy regimens included as comparators in OlympiAD

(capecitabine, eribulin and vinorelbine). However, it is unlikely that the comparator safety profile in OlympiAD fully reflects the safety profile for the requested treatment population. The safety claim was therefore overall uncertain.

7.10 The PBAC considered results for the ITT population were appropriate as the basis for the economic model, as proposed in the pre-PBAC response. The cost-utility analysis compared olaparib with chemotherapy in patients with HER2-negative, *BRCA*m mBC who had previously received chemotherapy, based on the corresponding the results of the OlympiAD trial. The PBAC considered the outcomes included in the economic model were associated with uncertainty due to the applicability of the trial comparators (paragraphs 7.5-7.6). In addition, the PBAC noted that the economic model presented in the submission included assumptions that were favourable to olaparib, particularly: modelled improved survival associated with olaparib despite no statistically significant OS benefit demonstrated in the OlympiAD trial, application of differential utilities for PFS1 and PFS2 between treatment arms, and underestimated costs associated with *BRCA* testing. The PBAC noted that when these assumptions were revised as proposed by the ESC, the ICER increased substantially, to $155,000 to < $255,000/QALY. The pre-PBAC response maintained that differential (treatment-arm specific) utilities for PFS1 were reasonable and consistent with the safety claim for olaparib and the acceptance of differential utilities for sacituzumab govitecan in PBAC's March 2022 consideration. The pre-PBAC response also argued that additional testing costs to account for *BRCA*m prevalence were not appropriate due to the substantial testing that already occurs in clinical practice. However the PBAC noted that the testing cost calculations account for a proportion of patients receiving testing in earlier settings but inappropriately were not adjusted to include costs for patients tested in the metastatic setting who do not have a *BRCA* pathogenic variant. The PBAC noted that the pre-PBAC response proposed a reduced price for olaparib and a revised base case including minor changes to *BRCA* testing costs, treatment-specific utility values for PFS2 (but not PFS1) and modelled OS based on the HR for OS from the OlympiAD trial (0.9), resulting in an ICER of $45,000 to < $55,000 per QALY.

7.11 The PBAC considered that although OS benefits in the submission's base case model were likely overestimated, it was reasonable for the model to assume some difference in survival given the demonstrated PFS1 and PFS2 benefit, the divergence in OS curves (which was maintained in the longer follow-up data), and because OS in the trial was likely to have been impacted by subsequent treatments not available in Australian clinical practice. The PBAC considered that the application of differential utilities for PFS1 favoured olaparib and contributed substantially to uncertainty in the modelled outcomes. The PBAC considered it was appropriate for the testing costs in the model to account for the total additional *BRCA* testing, including accounting for the number of tests needed to identify one patient classified as g*BRCA*m. The PBAC considered that the pre-PBAC response revised base case did not fully justify the use of treatment-specific utility values for PFS 1 and did not adequately account for total additional

BRCA testing costs. Therefore, the PBAC considered the ICER in the pre-PBAC response remained optimistic and likely to be underestimated. The PBAC noted that when the pre-PBAC price and the pre-PBAC revised approach to modelling OS was applied to the ESC respecified base case the ICER was reduced to $75,000 to < $95,000 per QALY.

7.12 The PBAC considered that the ICER remained high at the price proposed in the pre-PBAC response. The PBAC considered that although there was some uncertainty regarding the inputs to the model, the ICER would be brought into an acceptable range at a price resulting in an ICER of no more than $55,000 to < $75,000 per QALY, using inputs in the ESC respecified base case (as described in paragraph 6.69), but with the OS for olaparib estimated by applying the trial-based HR (0.9) to the chemotherapy OS curve as proposed in the pre-PBAC response (as described in paragraph 6.72), and effective prices applied for relevant subsequent treatments.

7.13 The PBAC noted that the financial estimates provided in the submission were based on the 'no prior chemotherapy' subgroup and considered it would be appropriate for the estimates to be amended to reflect the broader population, including patients with HER2-negative mBC with a confirmed *BRCA* mutation, who have received chemotherapy in the adjuvant/neoadjuvant or metastatic setting. The PBAC considered that the following aspects of the financial estimates required revision were:

- An increase from 63% to 95% of HR+ patients with prior (neo)adjuvant chemotherapy so as not to exclude patients with recurrent disease who have received chemotherapy in the metastatic setting.
- A reduction in the duration of treatment consistent with the economic evaluation for the ITT population.

The PBAC considered that with these changes the financial estimates would be acceptable.

7.14 In November 2023, when recommending olaparib for listing in high risk eBC, the PBAC advised that a Risk Sharing Arrangement (RSA) should be implemented given uncertainty with patient numbers and testing/treatment uptake (paragraphs 7.10 to 7.11 olaparib PSD, November 2023 PBAC meeting). The PBAC considered it would be appropriate for a RSA to be implemented given uncertainty with patient numbers and testing/treatment uptake and particularly treatment duration. The PBAC considered it would be reasonable for financial caps for the RSA for eBC to be increased to account for additional use in patients with mBC, and that the financial estimates (revised as per paragraph 7.13) would be a reasonable basis for the increase.

7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for olaparib:

a) Olaparib is expected to provide a modest, but clinically relevant improvement in

efficacy over placebo;

b) Olaparib is not expected to address a high and urgent unmet clinical need as there are alternative therapies available;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

7.17 The PBAC noted that a flow-on change to the existing olaparib eBC listings would be appropriate, adding the prescriber instruction alerting prescribers to one lifetime use regardless of disease staging and amending the gene 'mutation' wording to 'variant'.

Outcome:
Recommended

8 Recommended listing

8.1 Add new listing with new indication for mBC as follows:

MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
OLAPARIB						
olaparib 100 mg tablet, 56		NEW	2	112	5	Lynparza
olaparib 150 mg tablet, 56		NEW	2	112	5	Lynparza
Restriction Summary / Treatment of Concept:						
	Category / Program: GENERAL – General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners					
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)					
Prescribing rule level	**Administrative advice:** Patients may qualify for PBS-subsidised treatment under this restriction once only					
Prescribing rule level	**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.					
Prescribing rule level	**Administrative advice:** No increase in the maximum quantity or number of units may be authorised.					
Prescribing rule level	**Administrative advice:** No increase in the maximum number of repeats may be authorised.					
Prescribing rule level	**Administrative Advice:** Special pricing arrangements apply					
	Severity: Metastatic					
	Condition: Breast cancer					
	Indication: Metastatic breast cancer					
	Treatment Phase: Initial treatment					
	Clinical criteria:					
	The condition must be human epidermal growth factor receptor 2 (HER2) negative,					
	AND					

	Clinical criteria:
	The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene variant,
	AND
	Clinical criteria:
	Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less,
	AND
	Clinical criteria:
	Patient must have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting
	AND
	Clinical criteria:
	Patient must not have received PBS-subsidised treatment with this drug in any earlier line of treatment for breast cancer
	AND
	Clinical criteria:
	The condition must be triple negative breast cancer, or
	The condition must be hormone-receptor positive breast cancer and the patient has: (i) progressive disease after receiving endocrine therapy, or (i) been considered inappropriate for endocrine therapy
	AND
	Clinical criteria:
	The treatment must be the sole PBS subsidised systemic anti-cancer therapy for this indication.
	Prescribing instruction: 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.
	Prescribing Instructions: Treatment with this drug for this condition is restricted to one line of therapy at any disease staging for breast cancer (i.e. if therapy has been prescribed for early disease, subsidy under metastatic disease is no longer available).

Restriction Summary / Treatment of Concept:	
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have received previous PBS-subsidised treatment with this drug in the metastatic setting,
	AND
	Clinical criteria:
	The treatment must be the sole PBS subsidised systemic anti-cancer therapy for this indication
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving treatment with this drug for this condition

8.2 Amend the existing eBC listing as follows:

- Flow-on changes to the existing olaparib eBC listings by adding the prescriber instruction alerting prescribers to one lifetime use regardless of disease staging. Additions shown in italics and deletions shown in strikethrough.
- Revise "mutation" to "pathogenic variant".

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
OLAPARIB					
Olaparib 100 mg tablet, 56	14181J	2	112	5	Lynparza
Olaparib 150 mg tablet, 56	14208T	2	112	5	Lynparza

Restriction Summary / Treatment of Concept:		
		Category / Program: GENERAL – General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
Prescribing rule level		**Administrative advice:** Patients may qualify for PBS-subsidised treatment under this restriction once only.
		Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
		Administrative advice: No increase in the maximum quantity or number of units may be authorised.
		Administrative advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special pricing arrangements apply.
		Severity: Metastatic
		Condition: Breast cancer
		Indication: Early breast cancer
		Treatment Phase: Initial treatment
		Clinical criteria:
		The condition must be human epidermal growth factor receptor 2 (HER2) negative
		AND
		Clinical criteria:
		Patient must have received neoadjuvant or adjuvant chemotherapy
		AND
		Clinical criteria:
		The treatment must be adjuvant to surgical resection
		AND
		Clinical criteria:
		The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene ~~mutation~~ *pathogenic variant*
		AND
		Clinical criteria:
		Patient must have received neoadjuvant chemotherapy, and residual invasive cancer is confirmed in the breast and/or resected lymph nodes (pathological complete response was not achieved); or
		Patient must have received adjuvant chemotherapy for triple negative breast cancer, and has either: (a) node positive disease is present, (b) a primary tumour greater than 20 mm; or
		Patient must have received adjuvant chemotherapy for hormone receptor positive breast cancer, and has at least 4 positive lymph nodes
		AND
		Clinical criteria:
		The treatment must not be a PBS-subsidised benefit beyond the following, whichever comes first: (i) a total of 52 weeks of treatment (including any non-PBS-subsidised supply), (ii) disease recurrence. Mark any remaining repeat prescriptions with the word 'cancelled'; where (i)/(ii) has occurred

	AND
	Clinical criteria:
	The treatment must be commenced within 12 weeks of completing other therapy noting that other therapy can be any of the following therapy: (i) surgery, (ii) radiotherapy, (iii) chemotherapy
	AND
	Clinical criteria:
	The treatment must not be in combination with any of the following: (i) abemaciclib, (ii) pembrolizumab
	Prescribing Instructions: Retain all pathology imaging and investigative test results in the patient's medical records.
	Prescribing Instructions: *Treatment with this drug for this condition is restricted to one line of therapy at any disease staging for breast cancer (i.e. if therapy has been prescribed for early disease, subsidy under metastatic disease is no longer available).*

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.