

**5.12 TALAZOPARIB,  
Capsule 250 micrograms (as tosilate),  
Capsule 1 mg (as tosilate),  
Talzenna<sup>®</sup>,  
Pfizer Australia Pty Ltd.**

**1 Purpose of Application**

1.1 The submission requested a Section 85, Authority Required listing for talazoparib for treatment of patients with germline breast cancer susceptibility gene mutated (gBRCAm) human epidermal growth factor receptor negative (HER2-) locally advanced inoperable or metastatic breast cancer who have been previously treated with a taxane and/or an anthracycline in the (neo)adjuvant, locally advanced or metastatic setting. The PBAC has not considered talazoparib previously.

1.2 The listing was requested on a basis of a cost-utility analysis of talazoparib compared with single-agent chemotherapy (standard of care (SoC)), and a cost-minimisation analysis of talazoparib to olaparib. The key components of the clinical issue addressed by the submission are summarised below.

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

<b>Component</b>	<b>Description</b>
Population	Patients with breast cancer 1 or 2 susceptibility gene mutation (BRCA1/2m) human epidermal growth factor receptor (HER2)-negative (either hormone receptor positive or triple negative) advanced (locally advanced inoperable or metastatic) breast cancer who have been previously treated with a taxane and/or an anthracycline in the (neo)adjuvant, locally advanced or metastatic setting.
Intervention	Talazoparib 1 mg capsule taken once daily (OD) until progression or unacceptable toxicity
Comparator	Main comparator: Standard of care single-agent chemotherapy (capecitabine, eribulin, gemcitabine or vinorelbine) Near market comparator: Olaparib
Outcomes	Primary: Progression free survival (PFS), as determined by blinded independent central review (according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1) Secondary outcomes: Overall Survival (OS), objective response rate (ORR), duration of response, Health related quality of life (HRQoL) and safety.
Clinical claim	Talazoparib has superior efficacy and different, but non-inferior safety compared to standard of care single-agent chemotherapy. Talazoparib and olaparib have similar efficacy and safety.

Source: Table 1.1.1, p5 of the main submission

**2 Requested listing**

2.1 Suggestions and additions proposed by the Secretariat to the proposed restrictions are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TALAZOPARIB 1 mg capsule, 30	30	5	\$7,459.34 (Public) \$ [REDACTED] (Effective)	Talzenna Pfizer Australia Pty Ltd

<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Locally advanced or metastatic
<b>Condition:</b>	Breast cancer
<b>PBS Indication:</b>	Locally advanced or metastatic germline BRCA HER2-negative breast cancer
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The condition must be human epidermal growth factor receptor 2 (HER2) negative AND The condition must be inoperable AND Patient must have a positive germline BRCA1 or BRCA2 gene mutation AND Patient must be resistant to endocrine therapy and/or have received at least one previous chemotherapy regimen in the neo(adjuvant), locally advanced or metastatic setting AND The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must not have previously received PBS-subsidised treatment with a <i>poly ADP ribose polymerase (PARP)</i> inhibitor <del>Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing</del>
<b>Population criteria:</b>	<del>The patient must be 18 years or over.</del>
<b>Prescriber Instructions:</b>	<i>Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing</i>
<b>Administrative Advice:</b>	<i>No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised  Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i>

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TALAZOPARIB 0.25 mg capsule, 30	90	5	\$7,459.34 (Public) \$ [REDACTED] (Effective)	Talzenna Pfizer Australia Pty Ltd

<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Locally advanced or metastatic
<b>Condition:</b>	Breast cancer
<b>PBS Indication:</b>	Locally advanced or metastatic germline BRCA HER2-negative breast cancer
<b>Treatment phase:</b>	Initial treatment

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<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The condition must be human epidermal growth factor receptor 2 (HER2) negative  AND  The condition must be inoperable  AND  Patient must have a positive germline BRCA1 or BRCA2 gene mutation  AND  Patient must be resistant to endocrine therapy and/or have received at least one previous chemotherapy regimen in the neo(adjuvant), locally advanced or metastatic setting  AND  The treatment must be the sole PBS-subsidised therapy for this condition  AND  Patient must not have previously received PBS-subsidised treatment with a poly ADP ribose polymerase (PARP) inhibitor  AND  Patients must not receive more than 6 months of treatment under this restriction</p>
<b>Population criteria:</b>	Patient must be 18 years or older.
<b>Prescriber Instructions:</b>	Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing
<b>Administrative Advice:</b>	<p>No increase in the maximum quantity or number of units may be authorised  No increase in the maximum number of repeats may be authorised</p> <p>Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

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<b>Severity:</b>	Locally advanced or metastatic
<b>Condition:</b>	Breast cancer
<b>PBS Indication:</b>	Locally advanced or metastatic germline BRCA HER2-negative breast cancer
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined

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<b>Clinical criteria:</b>	<p>The condition must be human epidermal growth factor receptor 2 (HER2) negative AND The condition must be inoperable AND Patient must have a positive germline BRCA1 or BRCA2 gene mutation AND Patient must be resistant to endocrine therapy and/or have received at least one previous chemotherapy regimen in the neo(adjuvant), locally advanced or metastatic setting AND Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not develop disease progression while receiving treatment with this drug for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing</p>
<b>Population criteria:</b>	The patient must be 18 years or over older.
<b>Prescriber Instructions:</b>	<p>Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing</p> <p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug</p>
<b>Administrative Advice:</b>	<p>No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised</p> <p>Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

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<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The condition must be human epidermal growth factor receptor 2 (HER2) negative AND The condition must be inoperable AND Patient must have a positive germline BRCA1 or BRCA2 gene mutation AND Patient must be resistant to endocrine therapy and/or have received at least one previous chemotherapy regimen in the neo(adjuvant), locally advanced or metastatic setting AND</p>

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	<p><i>Patient must have previously received PBS-subsidised treatment with this drug for this condition</i></p> <p><i>AND</i></p> <p><i>Patient must not develop disease progression while receiving treatment with this drug for this condition</i></p> <p><i>AND</i></p> <p><i>Patients must not receive more than 6 months of treatment under this restriction</i></p> <p><i>AND</i></p> <p><i>The treatment must be the sole PBS-subsidised therapy for this condition</i></p> <p><i>Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing</i></p>
<b>Population criteria:</b>	<i>The patient must be 18 years or over older.</i>
<b>Prescriber Instructions:</b>	<p><i>Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing</i></p> <p><i>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug</i></p>
<b>Administrative Advice:</b>	<p><i>No increase in the maximum quantity or number of units may be authorised</i></p> <p><i>No increase in the maximum number of repeats may be authorised</i></p> <p><i>Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i></p>

DPMQs were revised based on a proposed ex-manufacturer price of \$4,132.60 (effective) and \$7,307.23 (published), and the applicable mark-ups and fees as at 1 July 2019

- 2.2 The submission proposed a Special Pricing Arrangement (SPA).
- 2.3 No clear continuing criteria were provided in the submission. The continuing criteria proposed were identical to the proposed initial treatment criteria (pp32 and 31 of the submission, respectively). The Pre-Sub-Committee Response proposed the continuing treatment criteria ‘Patient must not develop disease progression while receiving treatment with this drug for this condition’ for continuing treatment.
- 2.4 The proposed clinical criteria, that the patient must be resistant to endocrine therapy and/or have received at least one previous chemotherapy regimen in the (neo)adjuvant, locally advanced or metastatic setting, would allow heavily treated patients ( $\geq$  two prior chemotherapy lines) to be eligible for talazoparib. However, the Economics Sub-Committee (ESC) noted that the majority of patients in the EMBRACA trial had received  $\leq 1$  prior cytotoxic chemotherapy regimen (approximately 76%) for advanced disease with only 24% of patients having received  $\geq$  two prior cytotoxic chemotherapy regimens. No more than two prior cytotoxic regimens in the locally advanced and/or metastatic setting were allowed in the trial.
- 2.5 Most patients in the EMBRACA trial had an ECOG (Eastern Cooperative Oncology Group) status of 0 or 1 ( $\leq 2\%$  of patients in EMBRACA had an ECOG status of  $>1$ ). The ESC considered it may be appropriate for the restriction to specify an ECOG status of 0 or 1 given there was limited evidence provided for patients with ECOG status  $>1$ .
- 2.6 The Sponsor requested that grandfathering provisions apply for a small number of eligible gBRCAm HER2- advanced breast cancer patients already receiving talazoparib.

It was estimated in the submission that less than 500 patients are likely to require grandfathering treatment at the time of the proposed PBS-listing.

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

### **3 Background**

#### ***Registration status***

- 3.1 The submission was made under the TGA and PBAC parallel process arrangements. A registration application for talazoparib was lodged with the TGA on October 29, 2018. The proposed TGA indication is for the treatment of patients with gBRCAm HER2-locally advanced or metastatic breast cancer. The proposed TGA indication appeared broader than the eligibility criteria for the main EMBRACA trial as prior cytotoxic therapy (with a taxane/anthracycline) was not specified. At the time of PBAC consideration, a positive Delegate's Overview was available. The TGA indication is yet to be finalised. The Delegate's Overview stated that 'the delegate is seeking impartial advice from independent Australian clinical experts in the treatment of breast cancer regarding specification of prior therapies in the wording of the indication, and will consider any additional matters raised by the clinical experts'.

#### ***Medical Services Advisory Committee (MSAC) context***

- 3.2 PBS eligibility for treatment with talazoparib will rely on results of BRCA testing. The submission noted that an application was lodged by the sponsor to MSAC on 9 November 2018 to initiate the co-dependent assessment of the Poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi) talazoparib<sup>1</sup>. The MSAC application is scheduled for consideration as a minor submission at the November 2019 MSAC meeting (28 – 29 November 2019). In the key EMBRACA trial, BRCA status for the majority of patients (95%) was confirmed centrally using the Myriad BRCAAnalysis. The TGA clinical evaluation report (provided during the evaluation) noted that the companion diagnostic (BRCAAnalysis) had been approved by the FDA but is not licensed in Australia, and that currently, germline BRCA mutations are usually detected by a blood test which are generally laboratory developed tests. A confirmed PICO (Application 1507) has been published by MSAC for "Germline BRCA mutation testing to determine eligibility for olaparib treatment in patients with metastatic (stage IV) HER2- breast cancer".

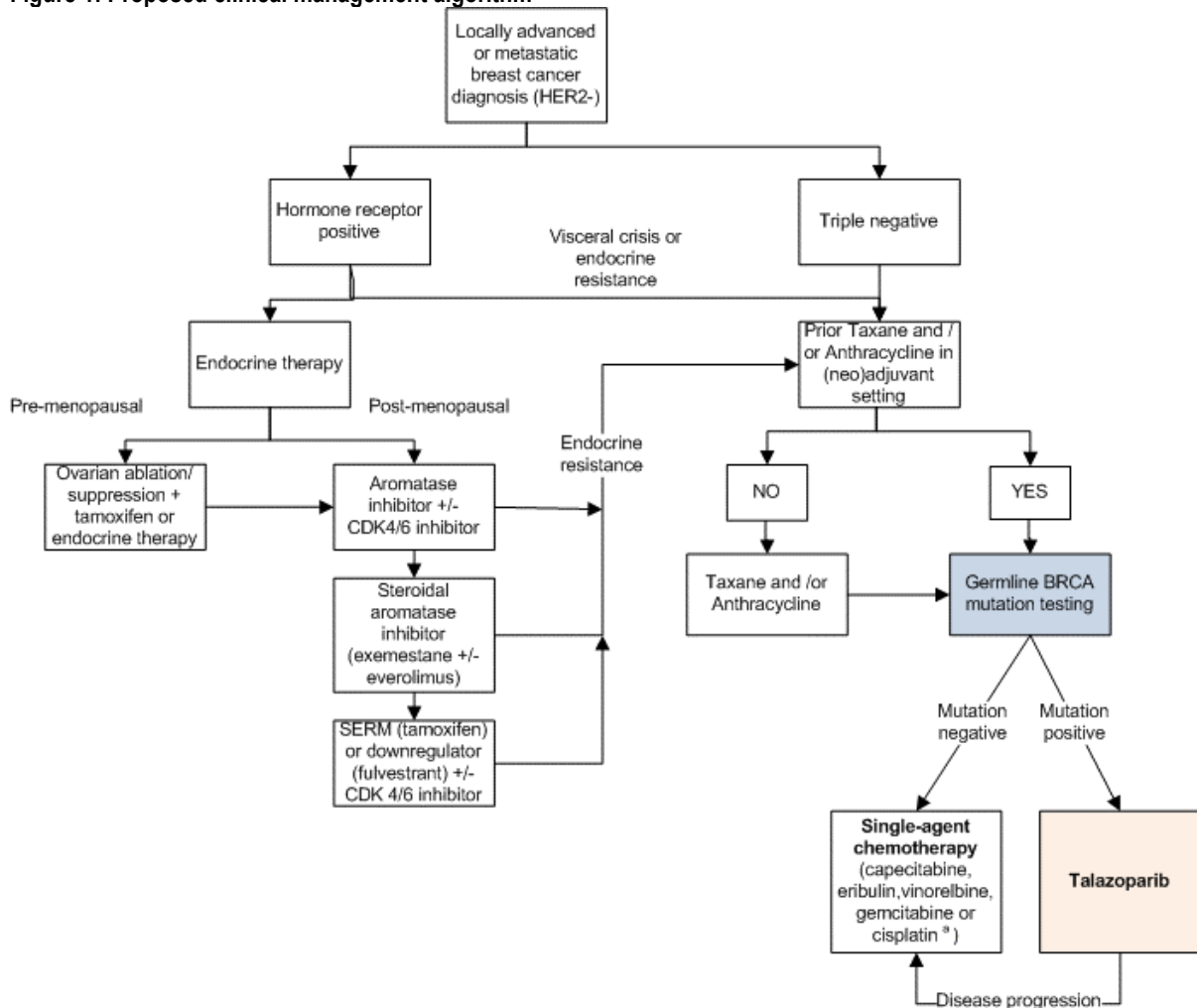
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<sup>1</sup> An application form was included in the references folder accompanying the submission titled: Germline BRCA mutation testing to determine eligibility for talazoparib treatment in patients with locally advanced or metastatic HER2-negative breast cancer (either hormone receptor positive or triple negative).

## **4 Population and disease**

- 4.1 Breast cancer is the most commonly diagnosed cancer among persons and females in Australia. A small proportion (<5%) of patients with advanced breast cancer will test positive for a gBRCA mutation (Meynard 2017, Fasching 2017). The prognosis for patients with germline BRCA mutated HER2–negative advanced breast cancer is poor, with a 5-year survival rate of less than 35%.
- 4.2 There are currently no PBS-listed treatments specifically targeted to germline BRCA mutated HER2–negative advanced breast cancer patients, for which the submission requested a PBS listing of talazoparib. The PBAC noted that there were a range of chemotherapy agents and endocrine therapies currently PBS-listed for this patient population. The PBAC also considered there was a clinical need for new treatments that result in cure or long-term remission, particularly for the sub-set of patients with the more aggressive triple negative form of breast cancer that are less responsive to currently available therapies.
- 4.3 The proposed clinical management algorithm is presented below.

Figure 1: Proposed clinical management algorithm



<sup>a</sup>. Some patients will have received treatment with cisplatin in the (neo)adjuvant setting

Sources for submission: NCCN Invasive breast cancer guidelines (Version 1.2019), ESMO 2018 Consensus Guidelines for Advanced Breast Cancer and PICO confirmation (Application 1507)

Source: Figure 1.2.2, p28 of the main submission

- 4.4 The ESC noted that immunotherapies, which are currently being trialled as a treatment for triple negative breast cancer may alter the clinical management algorithm in the future.
- 4.5 The ESC noted that while the proposed clinical management algorithm positioned germline BRCA mutation testing after treatment with a taxane/anthracycline in the neoadjuvant setting, some patients, including family members of those who have tested positive for a BRCA mutation, may undergo germline BRCA mutation testing earlier in the treatment algorithm. The ESC noted the impact on the treatment algorithm for patients tested earlier is unknown.
- 4.6 The ESC noted that many patients have currently not undergone germline BRCA mutation testing as MBS-funded testing is restricted to patients with high-risk clinical

and family history factors, and access to testing is not consistently available throughout Australia with only a limited number of cancer genetic services. The ESC considered there could potentially be access issues as an increase in demand for germline BRCA mutation testing is likely if talazoparib was PBS listed.

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

## **5 Comparator**

- 5.1 The submission nominated SoC, represented by single-agent chemotherapies such as capecitabine, eribulin, vinorelbine and gemcitabine, as the comparator for the proposed target population. The ESC considered that liposomal doxorubicin, nab-paclitaxel, and platinum-based chemotherapy are also relevant comparators in this treatment setting.
- 5.2 The submission did not consider platinum-based chemotherapy as part of SoC. This may be an alternative option in clinical practice. The ESC considered the nominated single-agent therapies to be representative of SoC with the exception of the exclusion of platinum-based chemotherapy. The ESC considered that platinum-based chemotherapy is part of current standard of care for patients with germline BRCA mutated HER2- negative breast cancer.
- 5.3 The submission also nominated olaparib (another active inhibitor of human PARP) as the near market comparator.

*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 considered there was a high clinical need for more effective therapies for gBRCAm HER2- advanced breast cancer, particularly for patients with triple negative breast cancer where it was stated that there were few effective treatment options following relapse. The clinician described the results of the EMBRACA trial, noting that the magnitude of PFS benefit was similar across subgroups within the trial, and that the early survival data could indicate a survival benefit associated with talazoparib compared to chemotherapy. The clinician emphasised treatment benefits of talazoparib such as improvement in quality of life, a tolerable side effect profile, and ease of administration.

- 6.2 In response to the Committee’s question regarding the use of platinum therapy, the clinician indicated a preference to use anthracyclines in the adjuvant setting, noting that the recommendation to use platinum therapy was based on the TNT trial<sup>2</sup>, which had a small number of patients with a germline BRCA mutation. However, the clinician acknowledged there was use of platinum therapy in this treatment setting. The clinician considered that talazoparib would be preferred over platinum therapy in the second-line setting, particularly for patients with the more rapidly progressing triple negative breast cancer, as these patients may not have the opportunity for third-line treatment.

### **Consumer comments**

- 6.3 The PBAC noted and welcomed the input from organisations (3) via the Consumer Comments facility on the PBS website. The Breast Cancer Network Australia (BCNA) and Pink Hope expressed their support for talazoparib to be made available to patients with gBRCAm HER2- locally advanced or metastatic breast cancer, noting there are limited effective treatment options available for these patients.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the talazoparib submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the EMBRACA trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for talazoparib, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>3</sup>, based on a comparison with single agent chemotherapy.

### **Clinical trials**

- 6.5 The submission was based on one head-to-head randomised trial (EMBRACA; N=431) comparing talazoparib with physician’s choice of single agent chemotherapy (SoC) in germline BRCA mutant patients with locally advanced inoperable and/or metastatic breast cancer. Enrolled patients had received prior treatment with a taxane and/or anthracycline in the (neo)adjuvant, locally advanced, or metastatic setting (unless they were medically contraindicated).
- 6.6 Details of the trial presented in the submission are provided in the table below.

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<sup>2</sup> Tutt A, Tovey H, Cheang MCU, et al: Carboplatin in BRCA 1/2-mutated and triple-negative breast cancer BRCAness groups: the TNT Trial. Nature Medicine 24(5):628-637,2018 <https://doi.org/10.1038/s41591-018-0009-7>

<sup>3</sup> 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 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Talazoparib versus main comparator single agent chemotherapy (standard of care (SoC))</b>		
Study C3441009 “EMBRACA”	A Phase 3, open-label, randomised, parallel, 2-arm, multi-centre study of talazoparib (BMN 673) versus physician’s choice in germline BRCA mutation subjects with locally advanced and/or metastatic breast cancer, who have received prior chemotherapy regimens for metastatic disease. Clinical Study Report: database lock September 2017.	March 2018
	Litton et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation.	<i>New England Journal of Medicine</i> 2018; 379(8):753-763
	Ettl et al. Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial.	<i>Annals of Oncology</i> 2018; 29(9):1939-1947
	Fasching et al. Impact of objective response (OR) on patient-reported outcomes (PRO) in patients (pts) with advanced breast cancer (ABC) and a germline BRCA1/2 mutation.	<i>Annals of Oncology</i> 2019; 30 (supplement 3): iii47-iii64
	Eiermann et al. Analysis of germline BRCA1/2 mutated (gBRCA) hormone receptor-positive (HR+) and triple negative breast cancer (TNBC) treated with talazoparib (TALA).	<i>Journal of Clinical Oncology</i> . Conference: 2018 Annual Meeting of the American Society of Clinical Oncology, ASCO 2018. United States. 36 (15 Supplement 1)
	Litton J. et al. EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline BRCA mutation. Cancer Research Conference	<i>San Antonio Breast Cancer Symposium</i> 2017; 78 (4 Supplement 1).

Source: Table 2.2.2, pp42-6 of the submission.

6.7 The key features of the direct randomised trial are summarised in the table below.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Talazoparib vs. SoC</b>						
EMBRACA	431	R, OL 14 months*	High	locally advanced inoperable and/or metastatic gBRCAm, HER2- breast cancer	PFS, OS	Used

SoC = standard of care; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; gBRCAm = germline BRCA mutation positive; HER2- = human epidermal receptor 2 (HER2)-negative

\*Median duration of 14 months for OS and 11 months for PFS.

Source: Compiled during evaluation based on data presented in Sections 2.3 and 2.4 of the submission.

6.8 Given the open label design of the trial, subjective outcomes, such as health-related quality of life (HRQoL) and drug-related adverse events (AEs), are subject to high risk of bias.

- 6.9 The primary analysis of progression-free survival (PFS) was based on blinded independent radiologic facility (IRF) review. There is a high degree of censoring in both arms in the analysis of IRF-based PFS (35.2% in the talazoparib arm and 42.4% in the SoC arm). The primary reason for censoring in the talazoparib arm was lack of disease progression or death events, censored at last tumour assessment date (20.6%). The primary reasons for censoring in the SoC arm were 1) discontinuation with no adequate post baseline tumour assessment (13%), and 2) no disease progression or death prior to start of new antineoplastic therapy (20.1%).
- 6.10 The lower number of recorded PFS events in the SoC treatment arm may have been the result of the higher rate of censoring in that arm due to patients initiating new antineoplastic therapy in the absence of IRF progression (20.1%), compared with the talazoparib arm (9.8%). As censoring was unlikely to be random, the assessment of comparative PFS is likely to be biased. The absolute magnitude of benefit of talazoparib in terms of PFS, compared with SoC, is therefore uncertain. The ESC acknowledged there was likely some impact of bias on the assessment of comparative PFS, however considered that the applicability issues raised in paragraphs 6.20 and 6.29 to be the main sources of uncertainty in the interpretation of the PFS results.
- 6.11 At the interim analysis for overall survival (OS), approximately 38% of patients had died in both treatment arms. OS data remain immature and the submission anticipated availability of mature OS data in November 2019. The pre-PBAC response stated that the final overall survival results for the EMBRACA trial are expected to be available in early January 2020. The TGA Delegate's Overview (p4) noted the potential for confounding by subsequent therapies in the final OS analysis.
- 6.12 A large proportion (82.4%) of patients did not receive platinum cytotoxic therapy before enrolment, and EMBRACA did not include platinum cytotoxic therapy as a potential comparator. A key publication reporting on the EMBRACA trial<sup>4</sup> noted that the failure to include platinum-based agents as an option in the standard-therapy group was a limitation of the EMBRACA trial, and that direct evidence comparing the efficacy and safety of a PARP inhibitor with platinum-based chemotherapy was lacking. The Pre-Sub-Committee Response (PSCR) stated that local market research data (from global market research firm IPSOS) estimated that 70% of Australian patients with metastatic triple negative breast cancer received platinum therapy as first-line treatment. The PSCR noted this was consistent with advice from Australian clinicians who confirmed that capecitabine, eribulin, vinorelbine and gemcitabine were the chemotherapy agents of choice in the proposed patient population. The ESC considered the exclusion of platinum-based chemotherapy as part of SoC, and lack of patients with prior platinum-based chemotherapy, were limitations in the applicability

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<sup>4</sup> Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee K-H, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *New England Journal of Medicine*. 2018;379(8):753-63

of the EMBRACA trial to the requested population, given platinum-based chemotherapy is part of current standard of care.

- 6.13 The ESC considered it was difficult to fully assess the applicability of the EMBRACA trial to the requested PBS population, as there are limited data on the Australian clinical practice setting. The ESC acknowledged that large studies may not be possible given the rarity of the disease.

### Comparative effectiveness

- 6.14 The PFS and OS results from EMBRACA are summarised below.

Table 4: PFS and OS outcomes from the EMBRACA trial.

	Talazoparib N=287	SoC N=144
<b>Primary endpoint: PFS</b>		
<u>Primary analysis: PFS by IRF</u>		
Events n (%)	186 (64.8%)	83 (57.6%)
• Radiographic progression	157 (54.7%)	68 (47.2%)
• Death	29 (10.1%)	15 (10.4%)
Censored	101 (35.2%)	61 (42.4%)
Duration of PFS (months) <sup>a</sup>		
• Median (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
• HR (95% CI): stratified <sup>b</sup>	0.54 (0.41, 0.71); p<0.0001	
PFS probability at month 12 (95% CI)	0.37 (30.7, 43.4)	0.20 (11.3, 29.9)
<u>Exploratory analysis: PFS by investigator assessment</u>		
Events n (%)	217 (75.6%)	102 (70.8%)
Censored	70 (24.4%)	42 (29.2%)
Median PFS duration in months, (95% CI)	7.0 (5.7, 7.6)	4.4 (2.9, 5.6)
HR (95% CI): stratified <sup>b</sup>	0.54 (0.42, 0.69)	
<b>Secondary endpoint: OS</b>		
<u>OS interim analysis</u>		
• Deaths n (%)	108 (37.6%)	55 (38.2%)
• Censored n (%)	179 (62.4%)	89 (61.8%)
○ Alive at analysis cutoff date	166 (57.8%)	65 (45.1%)
○ Loss to follow-up	13 (4.5%)	24 (16.7%)
Duration of OS (months)		
• Median (95% CI)	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
• HR (95% CI): stratified <sup>b</sup>	0.76 (0.55, 1.06); p=0.1053	
OS probability at month 12 (95% CI)	0.75 (68.6, 79.9)	0.73 (62.9, 80.4)

<sup>a</sup> Based on Kaplan-Meier estimates.

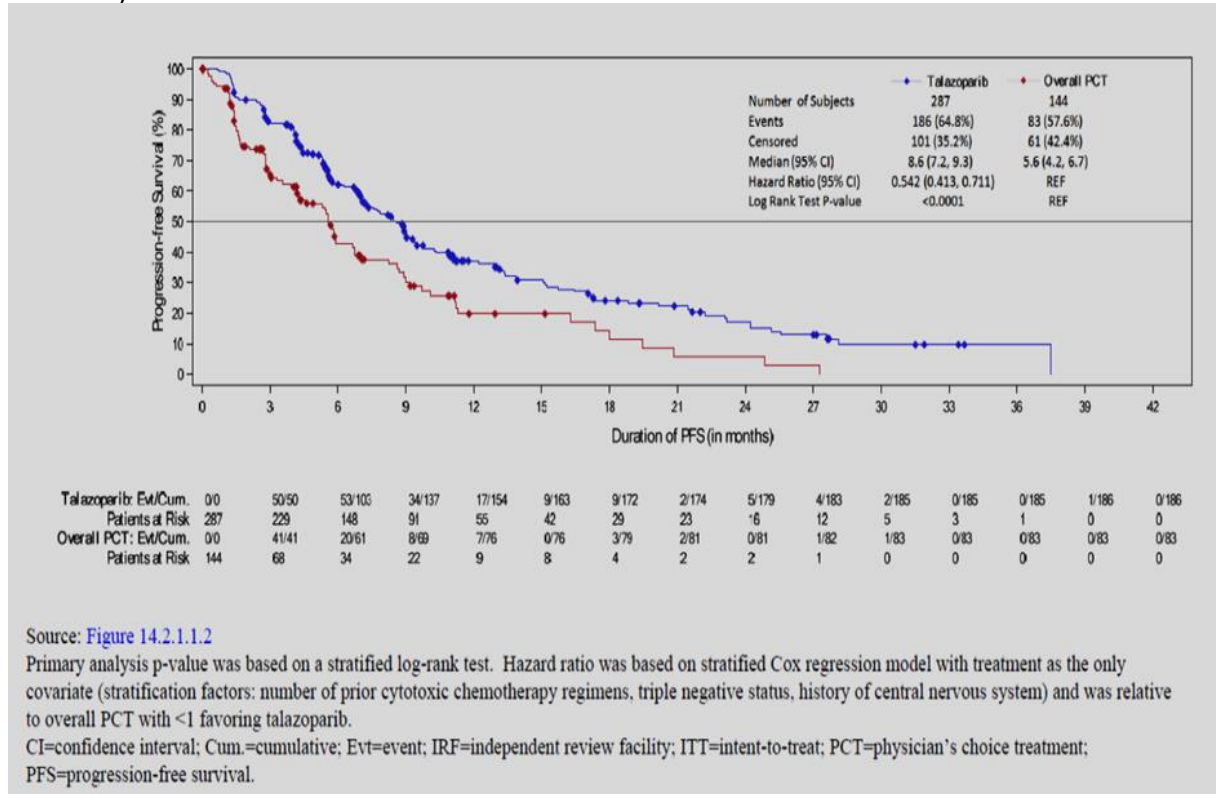
<sup>b</sup> P-value for the primary analysis was based on a stratified log-rank test. Hazard ratio was based on stratified Cox regression model with treatment as the only covariate (stratification factors: number of prior cytotoxic chemotherapy regimens, triple negative status, and history of central nervous system).

NR=not reached; CI=confidence interval; IRF=independent radiology facility; PFS=progression-free survival; OS=overall survival; SoC=standard of care (physician's choice of chemotherapy treatment)

Source: Table 2.5.1 and Figure 2.5.4 (pp80 and 89 of the main submission) and Section 11.4.2 of the EMBRACA CSR.

6.15 The Kaplan-Meier curves for progression-free survival and overall survival are presented in Figure 2 and Figure 3, respectively.

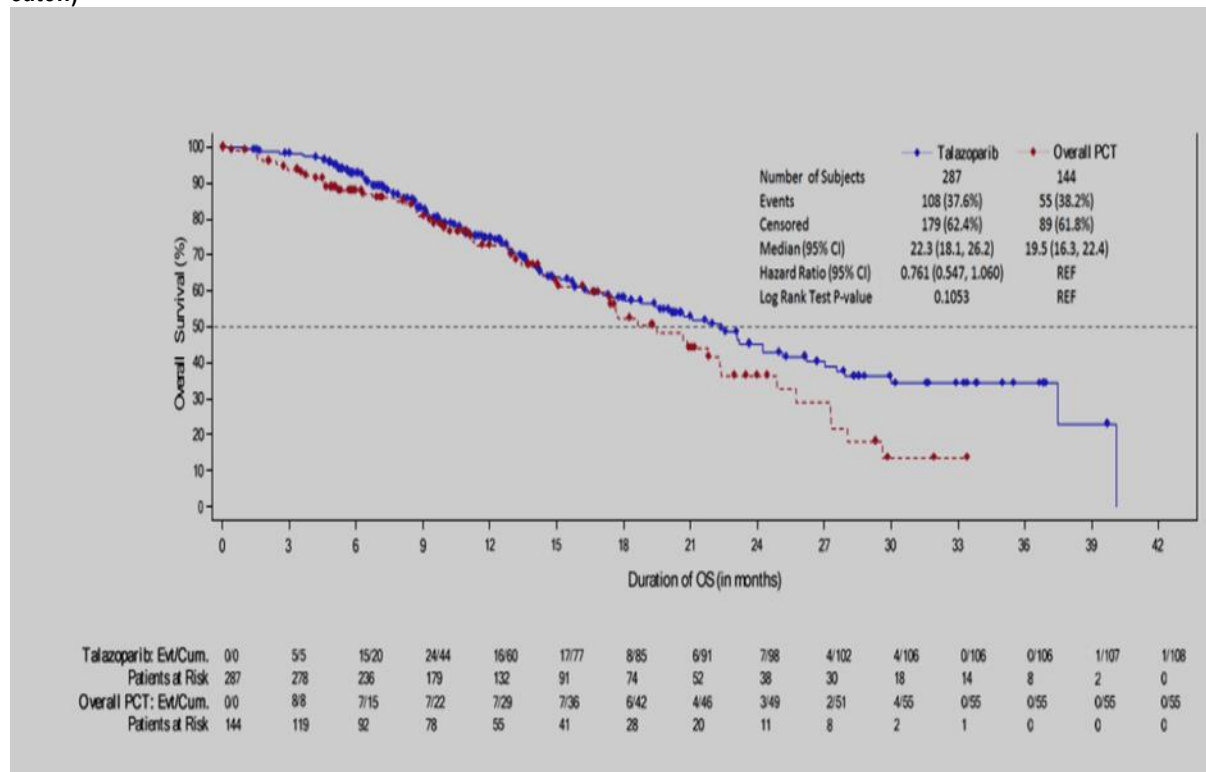
Figure 2: Kaplan-Meier survival curves for progression free survival by IRF (independent review) - September 2017 data cutoff)



CI=confidence interval; Cum.=cumulative; Evt=event; IRF=independent review facility; ITT=intent-to-treat; PCT=physician's choice treatment (referred to as standard of care (SoC) in the Commentary); PFS=progression-free survival

Source: Figure 8, p80, EMA European Public Assessment Report for talazoparib.

Figure 3: Kaplan-Meier curves of duration of overall survival (ITT Population) interim analysis - September 2017 data cutoff)



CI=confidence interval; Cum.=cumulative; Evt=event; ITT=intent-to-treat; PCT=physician's choice treatment (referred to as standard of care (SoC) in the Commentary); OS=overall survival

Source: Figure 9, p82, EMA European Public Assessment Report for talazoparib.

- 6.16 At the September 15 2017 data cut-off, with a median follow up duration of 11.2 months, the median duration of PFS was 8.6 months in the talazoparib arm (95% CI: 7.2, 9.3) and 5.6 months in the SoC arm (95% CI: 4.2, 6.7). Based on a stratified Cox regression analysis, the HR was 0.54 (95% CI: 0.41, 0.71;  $p < 0.0001$ ) in favour of the talazoparib arm. The estimated one year PFS rate was higher for the talazoparib treatment arm than for the SoC treatment arm (37% vs 20%).
- 6.17 The potential impact of censoring on the observed PFS results is unknown. Overall, 162 patients (37.6%) were censored from the primary IRF analysis (35.2% in the talazoparib treatment arm and 42.4% in the SoC treatment arm). It is unclear whether more patients in the SoC treatment arm being censored was because of change in treatment options (to other anti-neoplastic therapies), possibly due to clinical progressive disease/chemotherapy toxicity.
- 6.18 Investigator assessment (vs IRF assessment) resulted in a higher number of progression events or deaths in the talazoparib (75.6% vs 64.8%) and SoC (70.8% vs 57.6%) treatment arms, and a smaller benefit in median PFS duration (point estimate) between talazoparib and SoC (2.6 vs 3.0 months). Due to the censoring associated

with the initiation of a new antineoplastic therapy prior to IRF progression, PFS as determined by investigators may be more reliable than the more heavily censored IRF estimate.

- 6.19 The ESC considered that the benefit of talazoparib in clinical practice would likely be smaller than observed in the trial given the likely higher proportion of more heavily pre-treatment patients (including a higher proportion of patients treated with prior platinum cytotoxic therapy) in clinical practice. Further, the ESC considered that the incremental benefit of talazoparib compared with SoC would likely be smaller if platinum cytotoxic therapy was included in the SoC arm of the trial.
- 6.20 The pre-PBAC response noted that pre-specified subgroup analyses showed that the treatment effect versus chemotherapy, in terms of PFS, was similar across the subgroups of patients who had received 0, 1 and  $\geq 2$  prior chemotherapy regimens. Further, the pre-PBAC response noted that results of covariate analyses of the EMBRACA trial showed that prior platinum use did not significantly influence the treatment effect of talazoparib. The PBAC noted that, in subgroup analyses, the HR was higher for patients who had received previous platinum therapy versus those who had not (0.76 vs 0.52). The PBAC noted the analyses of platinum exposure on PFS were based on small patient numbers (only 17.6% of patients in the EMBRACA trial received prior platinum-based therapy, as patients with prior-platinum therapy were only eligible following a protocol amendment two-thirds of the way through the trial enrolment period) and that none of the analyses had been adjusted for multiplicity.
- 6.21 For the interim analysis of OS (data cutoff September 2017 with a median follow-up of 11.2 months), approximately 38% had died in both treatment arms with 62% of all patients censored. The proportion of patient's lost-to-follow was much less in the talazoparib treatment arm than in the SoC treatment arm (4.5% vs 16.7%). The difference in median OS was 2.8 months with a 14% reduction in hazard of death in favour of talazoparib, which was not statistically significant. The ESC considered that the magnitude of any incremental OS benefit could not be reliably determined given the immature data, noting that analysis and interpretation of interim OS data when an immature data-cut is analysed have been shown to be prone to systematic bias<sup>5</sup>. The ESC considered that the magnitude of any incremental OS benefit could not be reliably determined given the immature data.
- 6.22 Treatment with talazoparib improved overall mean change from baseline in global health status/quality of life (GHS/QoL) measured by EORTC QLQ-C30 (3.0 for talazoparib vs -5.4 for SoC;  $p < 0.0001$ ). Improvements were in terms of functional (i.e.

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<sup>5</sup> Bagust A, Beale SJ. Exploring the Effects of Early Censoring and Analysis of Clinical Trial Survival Data on Effectiveness and Cost-effectiveness Estimation through a Case Study in Advanced Breast Cancer. *Medical Decision Making*. 2018;38(7):789-96

physical, role, emotional, cognitive, social functioning, and body image) and symptom scales (i.e. fatigue, pain, insomnia, appetite loss, systemic therapy side effects, breast symptoms, and arm symptoms). These results should be interpreted in the context of the open-label design of the EMBRACA trial, the high proportion of censoring/missing data, and the uncertainty regarding the level of compliance with the HRQoL questionnaires over the duration of follow up. No significant differences were observed for any other scales.

## Comparative harms

6.23 The overall adverse events observed from EMBRACA are presented below.

**Table 5: Overview of safety in EMBRACA**

	Talazoparib (N=286) n (%)	SoC (N=126) n (%)	RD % (95% CI)	RR (95% CI)
Any TEAE	282 (98.6)	123 (97.6)	1.0 (-2.0, 4.0)	1.0 (0.9, 1.0)
Grade 3 or 4	193 (67.5)	80 (63.5)	4.0 (-6.0, 14.0)	1.1 (0.9, 1.2)
Related to study drug <sup>a</sup>	254 (88.8)	112 (88.9)	0.1 (-6.7, 6.5)	1.0 (0.9, 1.1)
Deaths due to TEAEs within 30 days	6 (2.1)	4 (3.2)	-1.0 (-4.5, 2.4)	0.7 (0.2, 2.3)
Serious TEAEs (Serious AEs)	91 (31.8)	37 (29.4)	2.5 (-7.2, 12.1)	1.1 (0.8, 1.5)
Serious AEs related to study drug <sup>a</sup>	26 (9.1)	11 (8.7)	0.4 (-0.6, 6.3)	1.0 (0.5, 2.0)
Grade 3-4 serious AEs	73 (25.5)	32 (25.4)	0.1 (-9.0, 9.3)	1.0 (0.7, 1.4)
Grade 3-4 serious AEs related to study drug <sup>a</sup>	159 (55.6)	61 (48.4)	7.2 (-3.3, 17.6)	1.1 (0.9, 1.4)
AEs associated with permanent study drug discontinuation	22 (7.7)	12 (9.5)	-1.8 (-7.8, 4.2)	0.8 (0.4, 1.6)
AEs associated with dose modification	190 (66.4)	75 (59.5)	6.9 (3.3, 17.1)	1.1 (0.9, 1.3)

<sup>a</sup> Assessed by the investigators as possibly, probably, or definitely related to study drug.

RD= risk difference; RR= relative risk; N=number of evaluable patients; n=number of patients in the category; SoC=standard of care (physician's choice treatment); TEAE=treatment-emergent adverse event.

For all percentages, the denominator is the number of patients in each treatment group within the safety population.

RD and RR values were calculated during the evaluation.

Source: Table 2.5.18, p116 of the submission and Table 33, p33 of the TGA clinical evaluation report

6.24 The frequency of treatment-emergent adverse events (TEAEs) was high in both the talazoparib and SoC treatment arms. The overall rates of serious TEAEs were similar (32% for talazoparib and 29% for SoC). The most common serious TEAEs in the talazoparib treatment arm (vs SoC) were anaemia (6% vs 0%), pyrexia (2% vs 2%), vomiting (2% vs 2%) and back pain (2% vs 1%). The most common serious TEAEs in the SoC treatment arm were pleural effusion (6%) and neutropenia (3%). The TGA clinical evaluation report noted (p35) that TEAEs that differed by >5% between the two treatment arms, and that were higher in the talazoparib treatment arm, included: anaemia, thrombocytopenia, fatigue, dizziness, and headache.

6.25 The overall rates of Grade 3-4 toxicities in EMBRACA were balanced between the talazoparib and SoC treatment arms (25.5% vs 25.4%), however there was a higher

rate of haematological Grade 3-4 toxicity in the talazoparib treatment arm (55% vs 38%). The ESC considered that overall, the safety of talazoparib and SoC was comparable.

## Benefits/harms

6.26 A summary of the comparative benefits and harms for talazoparib versus SoC is presented in the table below.

**Table 6: Summary of comparative benefits and harms for talazoparib versus SoC**

<b>Benefits</b>				
<b>Progression free survival (median duration of follow up 11 months) <sup>a</sup></b>				
<b>Event</b>	<b>Talazoparib</b>	<b>SoC</b>	<b>Absolute Difference</b>	<b>HR (95% CI)</b>
Progressed, n (%)	186/287 (64.8%)	83/144 (57.6%)		0.54 (0.41, 0.71) p<0.0001
Median PFS (months)	8.6	5.6	3	
% not progressed at 12 months (95% CI)	37% (30.7%, 43.4%)	20% (11.3%, 29.9%)	17%	
<b>Overall survival (median duration of follow up 14 months)</b>				
Deaths, n/N (%)	108/287 (37.6%)	55/144 (38.2%)		0.76 (0.55, 1.06) p=0.1053
Median OS (months)	22.3	19.5	2.8	
% Alive at 12 months (95% CI)	75% (68.6%, 79.9%)	73% (62.9%, 80.4%)	2%	

SoC=standard of care; PFS = progression-free survival; OS = overall survival; CI = confidence interval; HR = hazard ratio;

Source: Table 2.5.18 and Table 2.5.1, p80 and p116 of the submission and Table 33, p33 of the TGA clinical evaluation report

<sup>a</sup> Median durations of treatment of 6 months and 4 months for talazoparib and SoC, respectively

6.27 On the basis of direct evidence presented by the submission, for every 100 patients treated with talazoparib in comparison to SoC:

- Approximately 17 additional patients would remain progression-free at 12 months.
- The impact on OS is unable to be determined.
- A high but similar proportion of patient will experience AEs, although the types of AEs will differ. The most common SAE in the talazoparib arm was anaemia (6%) whereas the most common SAEs in the SoC arm were pleural effusion (6%) and neutropenia (3%).

## Clinical claim

6.28 The submission described talazoparib as superior in terms of effectiveness compared with single agent chemotherapy (referred to as SoC) and non-inferior “but different” in terms of safety compared to SoC.

6.29 The evaluation and ESC considered that the therapeutic conclusion presented in the submission in terms of efficacy was not adequately supported by the evidence presented in the submission.

- There are inadequate data on the relevant outcome of OS. Analyses of OS were interim-based with heavily censored data;

- The results indicated a PFS benefit associated with talazoparib. The EMBRACA trial met its primary endpoint, with a statistically significant increase of 3 months in the median PFS duration associated with talazoparib arm (median PFS 8.6 months) compared to the SoC arm (median PFS 5.6 months), as assessed by independent review. However, there is high uncertainty regarding the applicability of the results to clinical practice. In the EMBRACA trial, 38% of patients received no prior regimens for advanced or metastatic disease, 37% received one prior regimen, 20% received two prior regimens and 5% received  $\geq 3$  prior regimens. In Australian clinical practice, a higher proportion of more heavily pre-treated patients may receive talazoparib.
- The proportion of patients in EMBRACA who received carboplatin or cisplatin, as prior anti-neoplastic treatment for metastatic disease, was low in both arms (approximately 7.2% had prior carboplatin and 2.1% had prior cisplatin). The corresponding proportion of patients in Australian clinical practice, who would have had prior platinum therapy, is likely to be much higher given that local market research data (presented in the PSCR and pre-PBAC response) estimated that 70% of Australian patients with metastatic triple negative breast cancer received platinum therapy as first-line treatment. While the clinician who presented at the hearing indicated a preference for using anthracyclines (rather than platinum-based therapy) in the first-line metastatic setting, the PBAC noted the market research data indicated much higher use of platinum-based therapies in the first-line setting. This may impact the efficacy (and hence the cost-effectiveness) of talazoparib in the population for whom PBS listing is being sought.
- There was no platinum-based chemotherapy in the comparator arm of the EMBRACA trial. Thus, the efficacy of talazoparib versus platinum therapy is unknown. Where platinum is part of current standard practice for some patients, the cost-effectiveness of talazoparib is highly uncertain.

6.30 The PBAC considered the claim of superior comparative effectiveness was adequately supported by the data in terms of PFS, although the PBAC was uncertain whether the same extent of benefit would be observed in clinical practice (see paragraph 6.20). The PBAC considered that the data were not adequately mature to determine whether talazoparib would be associated with an OS benefit compared with SoC.

6.31 The PBAC considered the claim of non-inferior safety was reasonable.

### ***Economic analysis***

6.32 The submission presented an economic evaluation structured as a partitioned survival analysis based on the EMBRACA trial. The type of economic evaluation presented was

a cost-utility analysis and cost-effectiveness analysis (cost-per-life-year-gained). The key components of the economic evaluation are summarised below.

**Table 7: Summary of model structure and rationale**

<b>Component</b>	<b>Summary</b>
Time horizon	Seven years in the base case, with a range of 1-15 years for sensitivity analysis. This is compared with a median follow-up of 11.2 months for PFS, and 14.2 months for OS in EMBRACA.
Outcomes	Cost per Quality Adjusted Life Year (QALY) gained; Cost per Life Year (LY) gained
Method(s) used to generate results	Partitioned survival analysis.
Health states	Standard three health state model: Progression-free; Post-progression; Dead
Time interval over which outcomes and costs are allocated	Three weeks (21 days)
Health state allocation	Both the PFS and time on treatment (ToT; used to determine cost of treatment) Kaplan Meier curves from EMBRACA for both arms, were used directly in the model, without extrapolation, i.e. these estimates were assumed to decrease to zero at end of follow up. For OS, Kaplan Meier estimates were used until median follow up (14.2 months), then extrapolated using different parametric functions (log normal for talazoparib and Gompertz for SoC chemotherapy). AIC and BIC fit statistics were used to justify the choice of parametric function. There were a number of concerns regarding the allocation to health states. See comments below.
Software	Microsoft Excel for Office 365 (v1902); Excel 2010 compatible

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PFS = progression-free survival; OS = overall survival; ToT = time on treatment

Source: Table 3.1.1, Section 3 of the submission.

6.33 The key drivers of the model are summarised below.

**Table 8: Key drivers of the model**

Description	Method/Value	Impact
Extrapolation of OS	The modelled OS benefit in the extrapolated portion of the curves accounted for the vast majority (96%) of the total OS benefit in the model. The separation of the survival curves occurred after median follow up (14.2 months), and was based on immature data with heavy censoring in the earlier portion of the curves. The parametric functions were poorly justified.	High, favours talazoparib
gBRCA testing	The submission included gBRCA testing costs only for █% of treated patients (the remaining █% of patients were expected to already know their gBRCA mutation status), essentially omitting all those who tested negative and were not eligible for treatment with talazoparib.	Moderate, favours talazoparib
Treatment costs	The submission used the ToT curve from EMBRACA which was truncated at the end of follow up. This would underestimate the duration of treatment with talazoparib. The cost of talazoparib per cycle was adjusted based on an RDI of 91.7%. This was not appropriate given the flat pricing structure of the 0.75 mg/day and 1 mg/day dosing regimens. Furthermore, the submission did not allow for wastage. Wastage is likely to occur in practice as patients are dispensed an average of 30 days therapy (at a dose of 1 mg or 0.75 mg).	Moderate, favours talazoparib
Utilities	The submission did not provide adequate information to assess the appropriateness of the HRQoL data from EMBRACA that was used as the basis for the utility values in the progression-free health state.	Unclear

OS = overall survival; gBRCA = germline BRCA mutation; ToT = time on treatment; RDI = relative dose intensity; HRQoL = health-related quality of life.

Source: Compiled during the evaluation

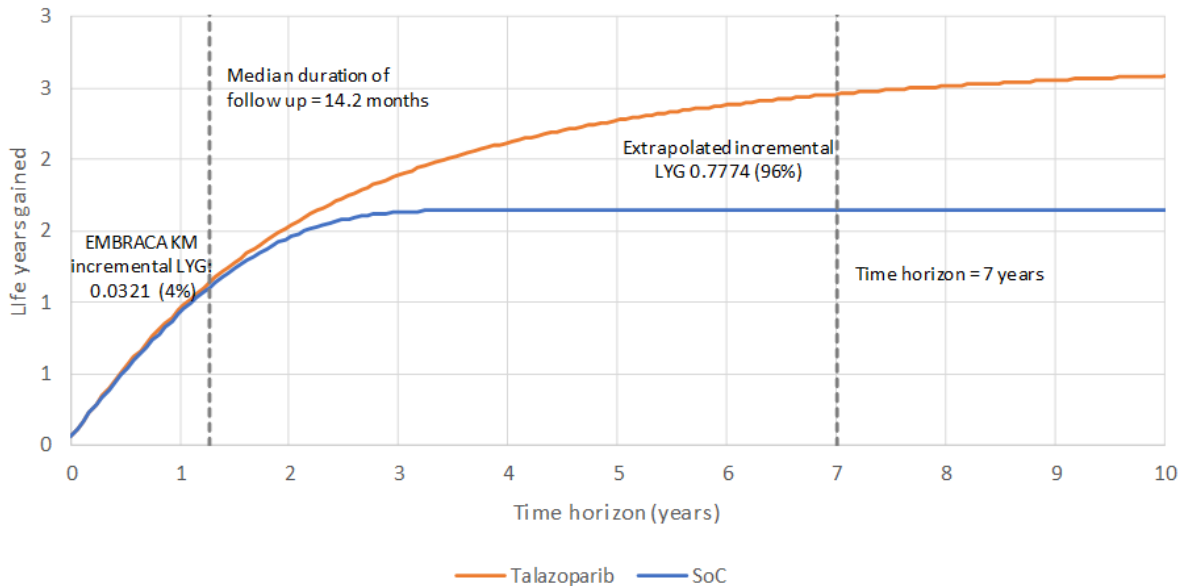
6.34 The extrapolation of OS curves in the model was based on immature OS data from EMBRACA, in which only about 38% of patients in both treatment arms had died within the follow-up period of the trial. Further, there was heavy censoring in the early portion of the curves. Therefore, the estimated OS benefit in the model was subject to high uncertainty. The ESC considered that more mature OS data would be required to accurately inform any incremental benefit in terms of OS of talazoparib vs SoC.

6.35 In addition, the selection of parametric functions to extrapolate the OS curves was poorly justified and the modelled long term OS benefit was not supported. The PSCR stated that parametric functions were selected based on the statistical goodness of fit (AIB/BIC). The ESC considered the clinical plausibility for the use of the chosen parametric functions to extrapolate OS was not adequately justified. The ESC noted that the selected parametric functions were not conservative (i.e. the Gompertz function used to extrapolate the SoC OS curve resulted in the most conservative OS extrapolation while the log normal function used for the talazoparib OS curve was more optimistic).

6.36 The modelled OS in the extrapolated portion of the curves accounts for the majority (96%) of the total OS benefit (in terms of life-years gained) in the model (see Figure 4 below). The ESC considered the magnitude of incremental OS benefit was not adequately justified by the available trial data given the trial data were immature and

there was uncertainty around the applicability of trial results to Australian clinical practice. The ESC also considered that the modelled incremental survival gain, which increased over the duration of the time horizon was not appropriate.

Figure 4: Cumulative life years gained over the time horizon of the model (undiscounted)



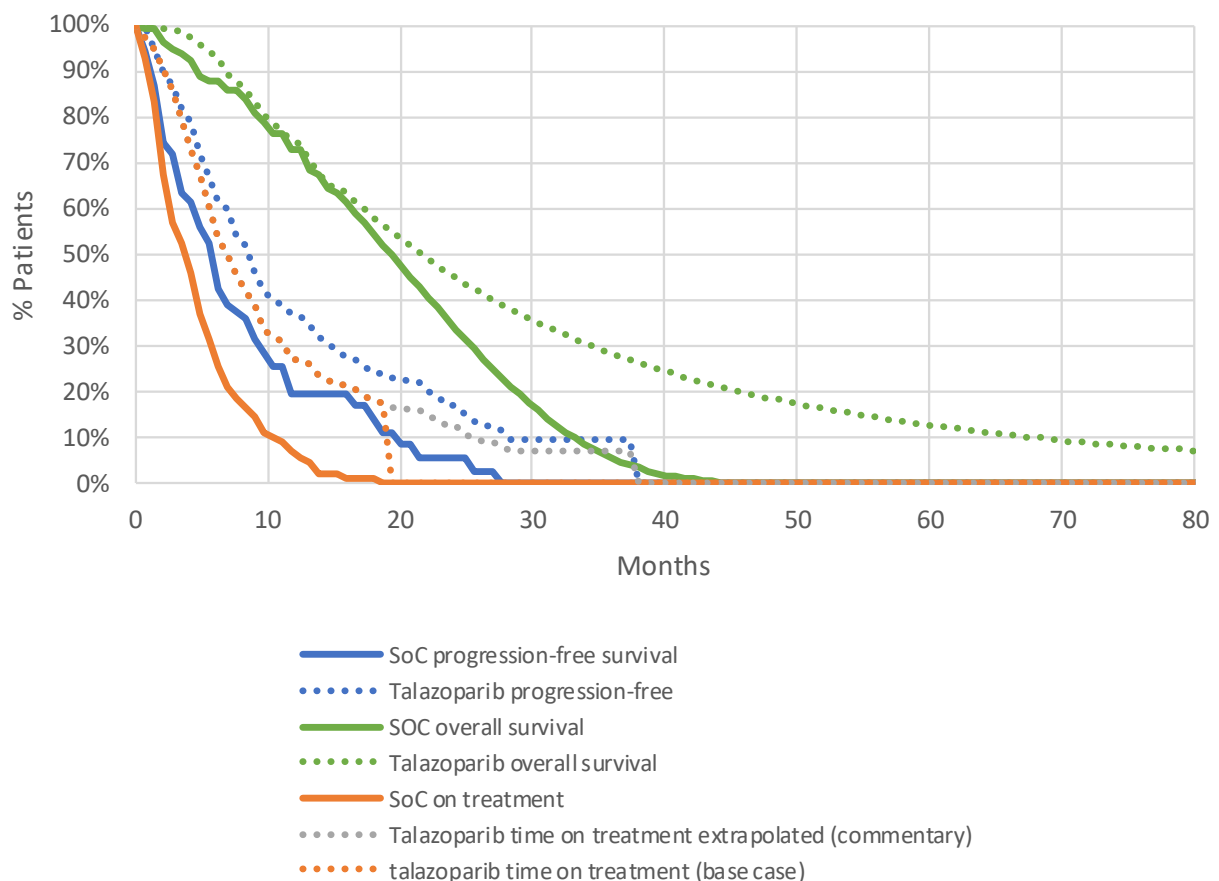
KM = Kaplan Meier; LYG = life years gained; SoC = standard of care  
 Source: compiled during the evaluation based on information presented in 'Talazoparib mBC CUA Australia.xlsx'

- 6.37 A time horizon of 7 years was used in the base case. The ESC noted that the PBAC previously accepted a time horizon of 3 years in its consideration of everolimus (July 2013) for the treatment of hormone-receptor positive HER2- advanced breast cancer and paclitaxel (November 2008) for the treatment of advanced breast cancer. The ESC also noted that the PBAC considered the time horizon of 10 years was too long in its consideration of palbociclib (March 2017) for the treatment of hormone receptor positive (HR+) HER2- advanced breast cancer where the median follow-up for a key trial (PALOMA-1) was 6.8 years.
- 6.38 The ESC considered that a shorter time horizon would be more appropriate given the uncertainties around the potential OS benefit due to the immaturity of the data. The ESC noted that the ICER increased from \$55,000 - \$75,000/QALY to \$75,000 - \$95,000/QALY when the time horizon was reduced to 5 years.
- 6.39 The submission used the time-on-treatment (ToT) Kaplan-Meier (KM) curves from the EMBRACA trial to inform the duration of treatment (median duration of follow up was not provided for ToT) for both the talazoparib and SoC arms in the model. At the end of follow-up for ToT, 17% of patients remained on treatment in the talazoparib arm, based on the ToT KM provided in the economic model. In the application of the ToT

KM curve for the talazoparib arm, the submission assumed that the proportion of patients on treatment at the end of follow up (17%) was immediately reduced to 0% on the next cycle, rather than extrapolating ongoing use. This was inappropriate and has likely underestimated the average cost of treatment with talazoparib. The PSCR acknowledged that using an extrapolated ToT curve which assumes the per-cycle probability of discontinuing treatment is equal to the probability of disease progression, as conducted by the evaluation (see Table 10 below) was reasonable. The ESC considered that while the application of the extrapolated ToT curve to the model was a more appropriate estimate of average cost of treatment with talazoparib, the estimated costs may still be an underestimate noting that the PFS curve is also truncated (see Figure 4).

6.40 The modelled PFS, OS and ToT for each of the arms (per the submission base case) are provided in Figure 5.

Figure 5: Modelled PFS, OS and ToT curves for the SoC and talazoparib arm (per the submission base case)



Talazoparib ToT – Extrapolated (Commentary): Sensitivity analysis assuming that the probability of discontinuing treatment over the cycle was equal to the probability of disease progression during that period.

Source: compiled during the evaluation based on information presented in 'Talazoparib mBC CUA Australia.xlsx'

- 6.41 The submission estimated that approximately █% of the treated population would be expected to know their germline BRCA status at model entry. The cited reference (IPSOS 2019) for this estimate was a physician survey conducted by the Sponsor. The only statistic relating to BRCA testing was the proportion of metastatic triple-negative breast cancer (TNBC) patients who underwent BRCA testing (approximately █%; N=█) in 2018 (Slide 40, IPSOS Breast Oncology Monitor █). It is unclear whether this sample is representative of patients with triple negative breast cancer in Australia, and whether this result could be generalised to patients with HR+ HER2- breast cancer. The submission then assumed that only the other █% of (to be talazoparib treated) patients will require germline BRCA testing to establish eligibility for treatment with talazoparib. The PSCR presented more recent data on the BRCA testing rate (IPSOS Healthcare oncology Monitor) for the second quarter of 2018 to the first quarter of 2019 which found that approximately █% of patients with triple negative breast cancer had been tested for a germline BRCA mutation. The ESC noted that these data were based on a small number of patients (█) with triple negative breast cancer only and was therefore uncertain that the results could be reasonably extended to patients with HR+ HER2- breast cancer. The ESC considered that the proportion of patients who would undergo testing was uncertain noting the current access issues associated with germline BRCA mutation testing (see paragraph 4.6).
- 6.42 The cost of germline BRCA mutation testing for patients considering therapy but subsequently found to be mutation negative were omitted. The ESC considered that the exclusion of the cost of testing for patients who are potentially eligible for talazoparib but test negative for a germline BRCA mutation was inappropriate and likely underestimated the total costs associated with listing talazoparib.
- 6.43 The submission used a relative dose intensity (RDI) of 91.7% to calculate the cost of talazoparib in the model. The application of the RDI to the price for the 1 mg capsule strength was inappropriate and may have underestimated the cost per cycle of talazoparib. The maximum quantity (90 capsules) of 0.25 mg capsules allows for 30 days of treatment at a dose of 0.75 mg/day. Given that the price per maximum quantity (3 packs, 90 capsules) of the 0.25 mg strength is equivalent to the price per maximum quantity (30 capsules) of the 1 mg strength, the cost per 30 days for an average dose of 0.75 mg/day and 1 mg/day is also equivalent. Therefore, without further information on the duration of dose reductions below 0.75 mg/day it would be reasonable to assume that the cost per 30 days for an average relative dose intensity of 91.7% would be equivalent to the cost of either 0.75 mg/day or 1 mg/day. The PSCR noted there was minimal use of the lower doses (0.25 mg and 0.5 mg) as the mean daily dose in the trial was 0.9 mg. The ESC considered that this further supports the use of the full DPMQ for each treatment cycle. The ESC considered that, given the flat pricing structure proposed, it would be incorrect to take account of dose

reductions simply by multiplying the RDI in the trial by the drug cost. The ESC considered that an RDI of 100% would be more appropriate in this case given the flat pricing, temporary nature dose reductions (dose modifications are only recommended to manage adverse drug reactions; and it is noted that the mean daily dose in the trial was 0.9 mg but 66% of patients in the talazoparib arm had an AE-associated dose modification) and the potential for wastage (e.g. there will be fewer days of treatment per 0.25 mg pack if the dose is increased to 1 mg/day). The pre-PBAC response indicated that it accepted the application of an RDI of 100% for talazoparib, as proposed by the ESC.

- 6.44 Utilities for the progression-free health state were based on the EORTC QLQ-C30 data collected from the EMBRACA trial. The CSR noted that up to treatment cycle 12, the percentage of eligible patients who completed at least 1 question on the EORTC-QLQ-C30 was 81% in the talazoparib arm and 73% in the PCT (SoC) arm. No other information was provided in the submission regarding completion rates of the QoL questionnaires over the duration of follow up. Without information on the extent of completeness of HRQoL follow up, it is difficult to assess any likely direction of bias. Furthermore, the open label nature of the trial may introduce bias into the utility estimates. Overall, the ESC considered there was limited information regarding how progression-free health state utilities were derived from the HRQoL data collected in the trial.
- 6.45 The submission based the post-progression utility value on an average of the reported progressive disease utilities for metastatic breast cancer from the studies identified through a systematic literature review. The utility value chosen for the progressive disease health state appeared reasonable and was consistent with other economic evaluations for advanced breast cancer considered by the PBAC. The ESC noted that the utilities have little impact on the ICER in the current model, however considered that utilities may have a larger impact on the ICER if the time horizon was reduced.
- 6.46 The results of the economic evaluation are presented below.

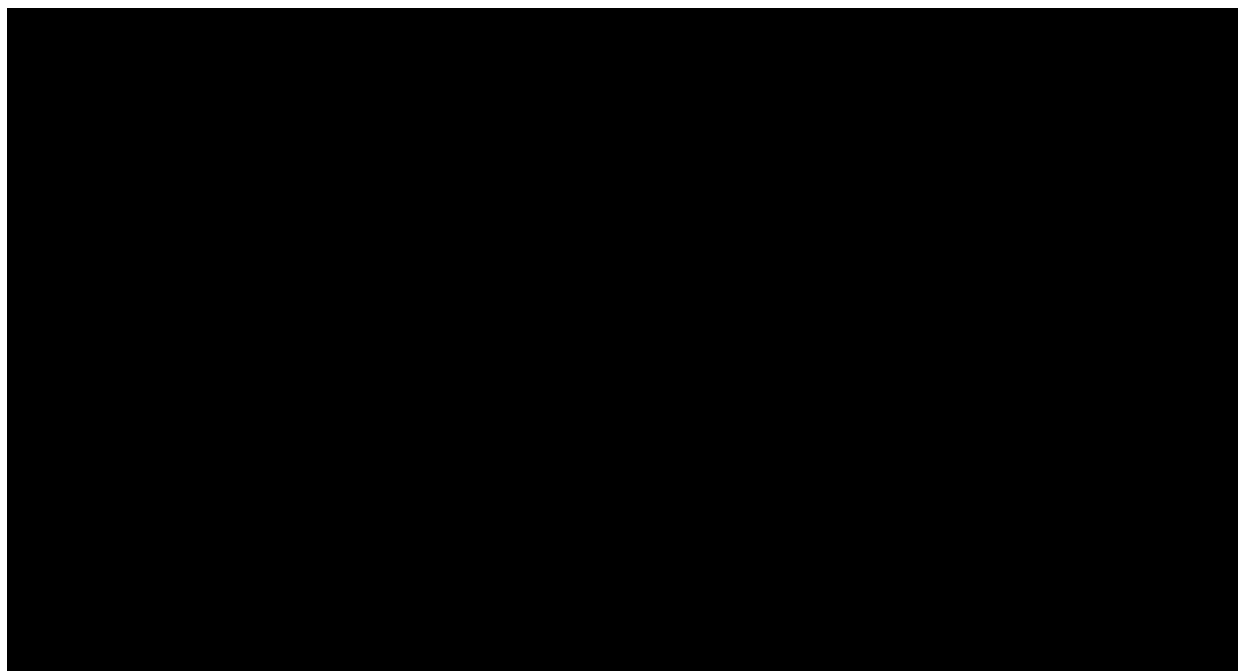
**Table 9: Results of the economic evaluation presented in the submission**

Outcome	Submission base case		
	Talazoparib	SoC	Incremental
Costs	\$ [REDACTED]	\$22,018	\$ [REDACTED]
Life Years	[REDACTED]	1.600	[REDACTED]
QALYs	[REDACTED]	0.908	[REDACTED]
Cost/LY	\$ [REDACTED]	\$13,757	\$ [REDACTED]
Cost/QALY	\$ [REDACTED]	\$24,246	\$ [REDACTED]
PSCR accepted base case: Incremental Cost/QALY			\$ [REDACTED]
ESC respecified base case, accepted by pre-PBAC response: Incremental Cost/QALY			\$ [REDACTED]

Source: Table 3.7.5, Section 3 of the submission

- 6.47 As noted above, given the highly uncertain OS benefit of talazoparib versus SoC in the model, the result of the economic evaluation was uncertain.
- 6.48 The ESC considered that the base case should be respecified to correct the costs associated with talazoparib treatment by incorporating the extrapolated ToT curve and an RDI of 100%. This resulted in an ICER of \$95,000 - \$115,000 per QALY. The pre-PBAC response considered the respecified base case to be reasonable.
- 6.49 The ESC considered that a shorter time horizon would further increase the ICER (see Figure 6).
- 6.50 Figure 6 provides a summary of the ICER (\$/QALY) over the time horizon of the model.

**Figure 6: Trace of the ICER (\$/QALY) over the time horizon of the model.**



Source: Constructed during the evaluation based on information presented in Talazoparib mBC CUA Australia.xlsx'

- 6.51 The key sensitivity analyses are presented below.

Table 10: Results of selected sensitivity analyses (based on the base case proposed by ESC which was and accepted in the pre-PBAC response)

Parameter (base case)	Value Tested	Incremental Costs	Incremental QALYs	ICER (\$/QALY)
Base case proposed by ESC and accepted in pre-PBAC response <sup>a</sup>		██████	██████	██████
<b>Costs of gBRCA testing</b>				
████% of treated patients tested	Approximately 16.38 patients would need to be tested in order to identify an additional patient with gBRCA mutations. Only applied to █████% of the treated population that were assumed to require testing <sup>b</sup>	██████	██████	██████
<b>Health state allocation: Extrapolation of OS</b>				
Extrapolation of OS curves (talazoparib arm: log-normal; SoC arm: Gompertz)	Weibull (both arms)	██████	0.2713	██████
	Log-normal (both arms)	██████	0.1596	██████
	Log-logistic (both arms)	██████	0.1881	██████
	Exponential (both arms)	██████	0.3078	██████
	Gompertz (both arms)	██████	0.3225	██████

<sup>a</sup> The cost of treatment with talazoparib is still likely to be underestimated. The extrapolated portion of the ToT curve is truncated at maximum follow up for PFS (see Figure 4 above). Furthermore, the submission's estimates did not account for potential wastage, as talazoparib is typically dispensed in a maximum quantity that allows for 30 days treatment at the recommended dose (i.e. a 30 capsule pack of 1 mg strength, at 1 mg/day), there would likely be wastage in practice.

<sup>b</sup> Including costs for █████% of patients who are treated, but would need to test to identify their mutation status upon PBS listing of talazoparib. Based on estimates in Section 4, the overall prevalence of gBRCA mutation was 6.10% in the HER2-negative breast cancer populations. This would mean that, on average, 16.38 patients would need to be tested to identify one additional gBRCA patient eligible for treatment with talazoparib. The average cost of the test (\$1200) was multiplied by the average number of patients to be tested to identify an additional case (16.38) for the █████% of the treated population who would not be expected to know their gBRCA mutation status. The cost of gBRCA testing included in the sensitivity analysis is still likely to be an underestimate, as those who are currently untested (i.e. lower risk patients) are likely to have a lower prevalence than the general HER2 negative breast cancer population.

Source: Compiled during the evaluation

6.52 The sensitivity analyses show that the results of the model were most sensitive to the following identified areas of uncertainty:

- The parametric functions used to extrapolate overall survival. The treatment benefit in the extrapolated portion of the OS curve remains highly uncertain given the immaturity of the OS data from EMBRACA.
- The inclusion of the cost of gBRCA testing for patients who test negative for gBRCA mutations. It should be noted that the prevalence of germline BRCA mutations in the estimated █████% of the population whose BRCA mutation status was assumed to be unknown at model entry may be lower than the general HER2- breast cancer populations used in the sensitivity analysis since high risk patients should have been tested under MBS Items 73296 or 73297. Therefore, the average number of patients who would need to be tested to identify an additional gBRCA mutation positive patient would likely be higher and this sensitivity analysis would not capture the full cost associated with gBRCA mutation testing. Therefore, this sensitivity analysis is still likely to underestimate the ICER.

6.53 The ESC considered that the true ICER/QALY was potentially higher than \$95,000 - \$115,000/QALY given uncertainties around the OS benefit and the costs associated with gBRCA mutation testing for patients who test negative, as outlined above. The ESC noted that the ICER/QALY increased to:

- \$115,000 - \$135,000/QALY when additional costs for gBRCA mutation testing were included; and
- over \$255,000 - \$355,000/QALY when OS was extrapolated using alternative functions and the model incorporated gBRCA mutation testing costs for patients who would test negative.

**Drug cost/patient/course**

6.54 The drug cost/patient/course is summarised below. The costs have been updated to reflect the drug cost changes accepted by the pre-PBAC response, as noted above.

**Table 11: Intervention and comparator costs per patient (undiscounted), medicine costs only**

	Talazoparib Trial dose and duration	Talazoparib Economic model	Talazoparib Financial estimates	SoC Trial doses and durations	SoC Economic Model	SoC Financial estimates
Mean dose	0.91 mg (1 mg * 91.7% RDI)			Capecitabine = 1250mg/m <sup>2</sup> * 83.3% RDI Eribulin = 1.40mg/m <sup>2</sup> * 90.5% RDI Gemcitabine = 1250mg/m <sup>2</sup> * 86.3% RDI Vinorelbine = 3mg/m <sup>2</sup> * 68.5% RDI		Capecitabine = 1250mg/m <sup>2</sup> Eribulin = 1.40mg/m <sup>2</sup> Gemcitabine = 1250mg/m <sup>2</sup> Vinorelbine = 3mg/m <sup>2</sup> BSA: 1.77m <sup>2</sup>
Mean duration (months)	8.4 <sup>a</sup>	11.0 months <sup>b</sup>	8.6 months (median PFS from EMBRACA)	Capecitabine = 5 Eribulin = 4.1 Gemcitabine = 4.7 Vinorelbine = 3.9	All regimens: 5.01	5.6 months
Cost/patient/30 days	██████	██████	██████	██████	██████	██████
Cost/patient/course	██████	██████	██████	██████	██████	██████

RDI = relative dose intensity; PFS = progression-free survival; BSA = body surface area; NR = not applicable; SoC = standard of care

<sup>a</sup> Table 25 of the EMBRACA CSR

<sup>b</sup> Per ESC's respecified base case, which was accepted in the pre-PBAC response: Time on treatment extrapolated beyond follow up in EMBRACA by assuming the per cycle probability of treatment cessation is equal to the per cycle probability of progression.

<sup>c</sup> Per ESC's respecified base case, which was accepted in the pre-PBAC response: Revised during the evaluation to account for the cost per dose between 0.75 mg and 1 mg. Cost per 30 days assumed equal to DPMQ of 30 capsule pack of 1 mg strength OR 90 capsule pack of the 0.25 mg strength (0.75 mg per day for 30 days) = \$██████.

<sup>d</sup> Assuming mean dose equal to target dose \* RDI, weighted by usage in EMBRACA, and a BSA of 1.8m<sup>2</sup>.

<sup>e</sup> Calculated during the evaluation by dividing the total cost of talazoparib to the PBS by the number of patients to be treated. Small differences between Section 3 and Section 4 estimates are likely to be due to rounding.

<sup>f</sup> Calculated during the evaluation by dividing the total cost offsets associated with comparator regimens by the total number of patients expected to be treated i.e. for year 1: \$647,354 / ██████ patients.

Source: Compiled during the evaluation, based on information presented in the Submission.

### **Estimated PBS usage & financial implications**

- 6.55 This submission was not considered by DUSC.
- 6.56 The submission used an epidemiological approach to estimate the financial impact of listing talazoparib on the PBS and expansion of an MBS Item for gBRCA mutation testing for eligibility to talazoparib.
- 6.57 The approach used to estimate the number of patients with HR+ HER2- breast cancer and TNBC appeared reasonable, and was broadly consistent with that previously accepted by the PBAC and DUSC for the March 2017 palbociclib submission. However, the submission inappropriately excluded approximately 5.9% of patients from the calculation of the number of breast cancer cases, primarily due to their unknown disease stage at diagnosis based on AIHW 2018 Cancer Data in Australia (5.5%). The remaining 0.4% ( $5.9\% - 5.5\% = 0.4\%$ ) of breast cancer patients that were excluded from the submission's estimates was likely due to a typographical error relating to the proportion of patients with Stage I-II disease at diagnosis.
- 6.58 The prevalence of gBRCA mutations in the HR+ HER2- and TNBC subpopulations were highly uncertain, given that the reported prevalence in these populations varied greatly in the literature.
- 6.59 It is likely that the submission has underestimated the cost per patient per course of talazoparib, and overestimated the cost offsets associated with the treatment of comparator regimens, due to the following:
- For talazoparib: The average duration of therapy was assumed to be equal to the observed median PFS in the EMBRACA trial (8.6 months). This is inappropriate and it is unclear why the submission used this estimate, when the ToT curve for EMBRACA was available and was used in the economic model. The submission assumed a relative dose intensity of 91.7% to calculate the cost of talazoparib. As noted in the economic section above, the application of the RDI to the price for the 1 mg capsule strength will underestimate the cost per cycle of talazoparib, given the flat pricing structure for the 1 mg 30 capsule pack and 0.25 mg 90 capsule pack. Furthermore, the submission did not allow for wastage associated with the unused portion of packs upon treatment cessation.
  - For comparator regimens: the average duration of therapy was assumed to be equal to the observed median PFS in the EMBRACA trial (5.6 months). Again, it would have been more appropriate to use the observed mean for the purposes of estimating total use. Although these regimens are available for use until progression, many patients would discontinue treatment due to notable adverse events associated with chemotherapy. Also, the submission assumed 100% relative dose intensity for all comparator regimens. This approach is inconsistent with the trial evidence that showed an RDI between 68.5% for vinorelbine and

90.5% for eribulin. This approach was also inconsistent with that used to cost talazoparib.

6.60 Similar to the economic model, the submission only included the cost of gBRCA mutation testing for those patients who test positive. This is inappropriate and underestimates the cost associated with gBRCA testing. It is likely that the prevalence of gBRCA mutations in those patients who are not currently covered by MBS Items 72396 and 73297 (i.e. currently untested) is lower than estimated in the general HR+, HER2- breast cancer population. The PSCR argued that the cost to the MBS for gBRCA mutation testing was conservatively estimated by including the cost of the test incurred by the total additional eligible advanced gBRCAm HER2- breast cancer population which was estimated to be 15% in year 1 increasing to 30% in year 6. The PSCR noted that this uptake is in addition to the estimated 50% of the proposed population who already have undertaken a gBRCA mutation test. The ESC noted that for the first year of listing, the submission only included the costs of gBRCA mutation testing for [REDACTED] patients who were expected to undertake testing and test positive. As not all patients tested would be expected to be positive, the ESC considered that the submission did not incorporate the testings costs for the total number of patients who would undertake gBRCA mutation testing to determine eligibility with talazoparib.

6.61 The submission assumed an uptake rate of talazoparib of 65% in year 1, increasing to 80% in years 4-6.

6.62 The estimated financial implications of listing talazoparib are summarised in Table 12.

**Table 12: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	■	■	■	■	■	■
Number of scripts dispensed <sup>a</sup>	■	■	■	■	■	■
<b>Estimated financial implications of talazoparib</b>						
Cost to PBS/RPBS	■	■	■	■	■	■
Copayments	■	■	■	■	■	■
Cost to PBS/RPBS less copayments	■	■	■	■	■	■
<b>Estimated financial implications for other medicines (standard of care)</b>						
Cost to PBS/RPBS	■	■	■	■	■	■
Copayments	■	■	■	■	■	■
Cost to PBS/RPBS less copayments	■	■	■	■	■	■
<b>Net financial implications</b>						
Net cost to PBS/RPBS	■	■	■	■	■	■
Net cost to MBS	■	■	■	■	■	■
Net cost to PBS/RPBS/MBS/ /other	■	■	■	■	■	■

<sup>a</sup> Assuming an average of 8 scripts (8.6 months duration; 8.73 packs 1 mg strength \* 91.7% RDI) per year as estimated by the submission.

\* ■ additional patients from Pfizer's Compassionate Access Program to be grandfathered onto PBS in Year 1 of PBS listing.

Source: Compiled during the evaluation based on information presented in Section 4 of the submission

The redacted table shows that at Year 6, the estimated number of patients was <500 and the net cost to the PBS would be \$0 – 10 million per year.

### **Quality Use of Medicines**

6.63 The sponsor detailed a number of activities designed to support the quality use of medicines, including:

- Provision of education materials for talazoparib to relevant health care professionals.
- Evidence-based information and other support for patients.

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

## **7 PBAC Outcome**

7.1 The PBAC did not recommend the listing of talazoparib for the treatment of patients with germline breast cancer susceptibility gene mutated (gBRCAm) human epidermal growth factor receptor negative (HER2-) locally advanced inoperable or metastatic breast cancer. The PBAC considered that although treatment with talazoparib provided a moderate benefit in terms of progression free survival (PFS), it was unclear given the immature data whether talazoparib would lead to any gains in overall survival (OS). The PBAC considered the modelled incremental OS benefit was optimistic and the ICER was unacceptably high, uncertain and potentially underestimated.

7.2 The PBAC acknowledged there is a clinical need for more effective therapies for patients with gBRCAm HER2- breast cancer, and that this need was highest for patients with the more aggressive triple negative form of breast cancer in whom outcomes remain poor despite the range of systemic therapies available. The PBAC noted that the majority of patients with a germline BRCA mutation would have triple negative breast cancer.

7.3 The PBAC considered that SoC single-agent chemotherapy represented by capecitabine, eribulin, vinorelbine and gemcitabine was an appropriate comparator. However, the PBAC considered it would have been appropriate for platinum therapy to be included in the group of comparator chemotherapy regimens, noting that the 2018 ESMO Consensus Guidelines recommend use of a platinum-based regimen for patients with BRCA-associated triple negative or endocrine-resistant metastatic breast cancer previously treated with an anthracycline with or without a taxane. The PBAC noted that the final TGA indication for talazoparib may provide more clarity around its place in the Australian clinical setting relative to platinum chemotherapy.

7.4 The PBAC noted the submission was based on the EMBRACA trial, which compared

talazoparib with physician's choice of single agent chemotherapy in patients with gBRCAm locally advanced inoperable and/or metastatic breast cancer. The PBAC noted that the median PFS was 8.6 (95% CI: 7.2, 9.3) and 5.6 months (95% CI: 4.2, 6.7) in the talazoparib and SoC arms respectively, with a hazard ratio for PFS of 0.54 (95% CI: 0.41, 0.71). The PBAC considered this represented a moderate benefit in terms of PFS, but was uncertain of the true magnitude of the treatment effect. The PBAC noted a higher proportion of patients in the SoC comparator arm were censored from the primary analysis for potentially informative reasons (i.e. discontinuation with no adequate post baseline tumour assessment and no evidence of disease progression or death prior to the start of new antineoplastic therapy). Further, the PBAC considered that the incremental treatment effect may be lower in Australian clinical practice as:

- platinum chemotherapy was excluded from the SoC comparator arm;
- few patients in the EMBRACA trial received prior platinum-based chemotherapy (17.6%), while local market research data estimated that 70% of Australian patients with metastatic triple negative breast cancer received platinum-based chemotherapy as first-line treatment (see paragraph 6.12); and
- the majority of patients in the EMBRACA trial received  $\leq 1$  prior cytotoxic chemotherapy regimen (75%), while in Australian clinical practice, the proportion of more heavily pre-treated patients may be higher (including patients who received previous platinum-based therapy, as noted above).

- 7.5 The pre-PBAC response provided the results of pre-specified subgroup and covariate analyses on PFS across previous lines of chemotherapy regimens (0, 1 or  $\geq 2$  prior cytotoxic regimens) and prior platinum use. However, the PBAC considered there were limitations associated with these analyses (see paragraph 6.21). Overall, the PBAC considered there were insufficient data to determine the extent to which the following factors impacted on the treatment effect of talazoparib: the exclusion of platinum therapy from the SoC comparator arm; the limited number of patients with prior platinum chemotherapy in the trial; and the likely fewer heavily pre-treated patients compared to Australian clinical practice.
- 7.6 The PBAC agreed with the ESC that it was unclear given the immature data whether talazoparib would lead to any gains in overall survival (OS). The PBAC considered the OS data beyond the median 14-month follow up for OS to be unreliable, given the high proportion of censoring in both treatment arms. The PBAC noted that OS was not statistically significant at the interim analysis (HR 0.76, 95% CI 0.55, 1.06) of the EMBRACA trial; and after 12 months, 75% of patients were alive in the talazoparib arm versus 73% in the SOC arm. The PBAC noted the final OS results for the EMBRACA trial are expected in early January 2020.
- 7.7 The PBAC considered that the claim of non-inferior safety compared with SoC was reasonable overall, noting that most grade 3-4 AEs in the talazoparib arm were hematologic laboratory abnormalities that were managed with dose reductions or

interruptions.

- 7.8 The PBAC noted that treatment with talazoparib was associated with a statistically significant improvement in quality of life compared to SoC measured by EORTC QLQ-C30 (overall mean change in scores from baseline was 3.0 for talazoparib versus -5.4 for SoC;  $p < 0.0001$ ). The PBAC acknowledged these results should be interpreted in the context of the open-label design of the EMBRACA trial, the high proportion of censoring/missing data, and the uncertainty regarding the level of compliance with the HRQoL questionnaires over the duration of follow up.
- 7.9 The PBAC noted that a respecified base case of the economic model, which corrected for the costs of treatment with talazoparib, was proposed by the ESC and accepted by the pre-PBAC response, and resulted in an ICER of \$95,000 - \$115,000/QALY (compared to the base case ICER presented in the submission of \$55,000 - \$75,000/QALY). While the PBAC considered the changes made to the model in the respecified base case analysis were appropriate, it considered the ICER to be unacceptably high.
- 7.10 The PBAC considered the ICER was underestimated due to uncertainties around the modelled OS benefit and time horizon, noting that the ICER was sensitive to the choice of parametric function used to extrapolate the OS curves and the time horizon. The PBAC noted the majority of OS benefit in the model occurs beyond the median follow up for OS in the trial, and that extrapolation of OS curves was based on a small number of events. The PBAC considered the modelled incremental gain was implausible on the basis of the PFS and OS data available (i.e. the PBAC considered the selected parametric function was poorly justified, and it was inappropriate for the modelled incremental survival gain to increase over the duration of the time horizon). The PBAC advised that more mature OS data would be required to determine the most appropriate OS extrapolation method and time horizon to reliably inform the cost-effectiveness of talazoparib.
- 7.11 The PBAC also considered that the costs of gBRCA mutation testing were underestimated in the economic model. The PBAC considered that the exclusion of testing costs for patients who do not test positive for a germline BRCA mutation was inappropriate. In addition, the PBAC agreed with the ESC that the proportion of the eligible patient population who would already know their germline BRCA mutation status was likely lower than assumed in the submission noting there were currently access issues to genetic testing due to the limited availability of genetic cancer services throughout Australia.
- 7.12 The PBAC considered the financial implications were underestimated in terms of gBRCA mutation testing costs and the cost per patient of talazoparib. The PBAC noted that the costs of gBRCA mutation testing for patients who would not test positive were not incorporated. The PBAC also noted the average duration of therapy with

talazoparib was assumed to equal the median PFS from the trial, which would underestimate the duration of therapy with talazoparib. The PBAC considered it would have been more appropriate to use the extrapolated time-on-treatment curve as per the respecified economic model to estimate the duration of therapy. The PBAC further noted that a relative dose intensity of 91.7% was inappropriately applied to the cost of the 1 mg strength capsules (see paragraph 6.58). The PBAC considered that while the eligible patient population was relatively small, there may be an increase in patient numbers if gBRCA mutation testing is subsidised for patients with HER2- breast cancer.

- 7.13 The PBAC advised that any resubmission would need to be a major resubmission. It should provide updated OS data from the EMBRACA trial, and address the issues around the time horizon, other aspects of the economic model, and financial implications noted above.
- 7.14 The PBAC considered that an initial treatment restriction for the 0.25 mg strength capsule would be required, as the recommended daily dose for patients with moderate renal impairment is 0.75 mg.
- 7.15 The PBAC considered that initial and continuing treatment phases should provide up to 6 months of treatment, and considered that a maximum quantity of 1 pack (containing 30 capsules) with 5 repeats would be appropriate for both the initial and continuing treatment phases. The PBAC noted this would provide 6 months of treatment for patients on the 1 mg/day dose and 2 months of treatment for patients on the 0.75 mg/day dose in each treatment phase. The PBAC considered that for patients on 0.75 mg/day, an increase in the maximum quantity of 0.25 mg capsules to provide up to 6 months of treatment should be permitted.
- 7.16 The PBAC considered that continuing treatment should be restricted to patients with stable or responding disease according to the Response Evaluation Criteria in Solid Tumours (RECIST), which was used to evaluate disease progression in the trial.
- 7.17 The PBAC agreed with the ESC that treatment with talazoparib should be restricted to patients with an Eastern Cooperative Oncology Group (ECOG) status of  $\leq 1$  noting there was limited evidence in the trial for patients with an ECOG status of  $> 1$ .
- 7.18 The PBAC considered that the proposed restriction criteria 'Patient must be resistant to endocrine therapy and/or have received at least one previous chemotherapy regimen in the (neo)adjuvant, locally advanced or metastatic setting' could be amended to 'Patient must have received prior chemotherapy in the adjuvant or metastatic setting' as the PBAC considered it would be appropriate to allow treatment with talazoparib, irrespective of prior chemotherapy agent.
- 7.19 The PBAC noted that the sponsor requested that grandfathering provisions apply for a small number of eligible gBRCAm HER2- advanced breast cancer patients already receiving talazoparib. However, the PBAC considered that separate restrictions for

grandfathered patients would not be required as grandfathered patients should be able to qualify under the proposed initial treatment restriction.

7.20 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

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

## **9 Sponsor's Comment**

The sponsor had no comment.