

## 5.08 OLAPARIB, 50 mg capsule, 4 x 112, Lynparza<sup>®</sup>, AstraZeneca Pty Ltd

### 1 Purpose of Application

- 1.1 The submission requested an Authority Required (Streamlined) listing for the maintenance treatment of women with a *BRCA1* or *BRCA2* gene mutation (*BRCAm*) and platinum-sensitive relapsed ovarian cancer, who are in response (complete or partial) to their most recent platinum-based chemotherapy regimen (e.g. carboplatin or cisplatin). Olaparib is intended for use as a maintenance therapy, administered after platinum-based chemotherapy, to extend the time to subsequent disease progression and extend overall survival.

### 2 Requested listings

- 2.1 Below is the Secretariat suggested restriction, additions are in italics and deletions are in strikethrough, including further suggestions by the PBAC.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
OLAPARIB Tablet 50 mg, 448	1	2	\$ [REDACTED]	Lynparza <sup>®</sup> AstraZeneca

<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>	<i>High grade serous</i>
<b>Condition:</b>	<i>Ovarian cancer, fallopian tube cancer, primary peritoneal cancer</i>
<b>PBS Indication:</b>	<i>High grade serous ovarian cancer, High grade serous fallopian tube cancer, High grade serous primary peritoneal cancer</i>
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

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<b>Clinical criteria:</b>	<p><i>The condition must be platinum sensitive</i></p> <p>AND</p> <p><i>Patient must have received at least two previous platinum-containing regimens</i></p> <p>AND</p> <p><i>Patient must have relapsed following a previous platinum-containing regimen</i></p> <p>AND</p> <p><i>Patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen</i></p> <p>AND</p> <p><i>The treatment must be as monotherapy</i></p> <p>AND</p> <p><i>The treatment must be maintenance therapy</i></p> <p>AND</p> <p><i>Patient must not have previously received PBS-subsidised treatment with <i>this drug</i> for this condition.</i></p>
<b>Population criteria:</b>	<p><i>Patient must have evidence of a germline class 4 or 5 BRCA1 or BRCA2 gene mutation.</i></p>
<b>Administrative Advice:</b>	<p><i>Platinum sensitivity is defined as disease progression greater than 6 months after completion of the penultimate platinum regimen.</i></p> <p><i>A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIG) or Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.</i></p> <p><i>Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline testing.</i></p>

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<b>Severity:</b>	High grade serous
<b>Condition:</b>	Ovarian cancer
<b>PBS Indication:</b>	High grade serous ovarian cancer
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have previously received PBS-subsidised treatment with <i>this drug</i> for this condition</p> <p>AND</p> <p>The treatment must be as monotherapy</p> <p>AND</p> <p>The treatment must be maintenance therapy</p> <p>AND</p> <p><del>Patient must not have progressive disease. Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST).</del></p>

- 2.2 The ESCs noted the PSCR (page 5) assertion that based on the advice from clinical experts, it may be impractical to incorporate the Response Evaluation Criteria in Solid Tumours (RECIST) into the continuing restriction to determine progression. The PSCR claimed that radiologists do not routinely report RECIST measurements outside of clinical trials, and that the use of RECIST could inadvertently necessitate additional health care resource during maintenance treatment, as scans may be required to be performed more frequently to exclude progression. The ESCs agreed that the use of RECIST to determine progression may be impractical, and noted that in Australia CA125 monitoring is frequently used for assessment. The ESCs advised that relative influence of CA-125 and imaging on decisions relating to disease progression remains unclear, and that this could be expected to contribute to a prolongation of olaparib treatment compared to the results of Study 19.
- 2.3 The ESCs considered there was a low likelihood of oncologists prescribing olaparib to patients other than those specified in the restriction, and thus considered that an Authority required (in writing) may not be necessary.
- 2.4 Listing was requested on a cost-effectiveness basis.

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

### **3 Background**

- 3.1 Olaparib was granted orphan drug designation by the TGA on 15 January 2015.
- 3.2 The submission was made under TGA/PBAC Parallel Process. Olaparib was approved by the TGA on 23 December 2015.
- 3.3 The TGA-approved indication for olaparib is as follows:

Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.
- 3.4 This is the first consideration by the PBAC of an application for PBS funding for olaparib maintenance treatment for women with *BRCA*m platinum-sensitive relapsed ovarian cancer.

### **4 Clinical place for the proposed therapy**

- 4.1 The submission stated that the majority of women with high-grade serous ovarian cancer (including fallopian tube or primary peritoneal) receive primary debulking surgery in combination with intensive first-line platinum-based chemotherapy. More than 70% of these patients relapse and require further retreatment with repeat courses of chemotherapy within the first three years of diagnosis.
- 4.2 Platinum-sensitive relapsed ovarian cancer is an uncommon condition which is life-threatening and affects women. The prevalence of a *BRCA* mutation is high amongst this group of patients (53.5% in Study 19).
- 4.3 The proposed listings are intended to be used in the third-line or later, following initial relapse (first line or later) and then response (second line or later) to prior platinum-based chemotherapy. These patients have limited options available to them and therefore have unmet clinical needs.

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

### **5 Comparator**

- 5.1 Standard follow-up care (placebo). The ESCs agreed that this was the appropriate comparator for olaparib.

*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 presenting at the hearing focused on the statistical analyses conducted as part of Study 19. The PBAC considered that the hearing did not add substantively to the evidence presented in the submission.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (28), and organisations (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with olaparib, including potential extension of the period of remission (hence delaying the need for chemotherapy) and improved overall survival. Olaparib was considered to have fewer side effects compared with chemotherapy.
- 6.3 The PBAC noted the advice received from Medical Oncology Group of Australia, Rare Cancers Australia, Ovarian Cancer Australia and Centre for Community Driven Research, clarifying the likely use of olaparib in clinical practice. The PBAC specifically noted the advice that the use of olaparib may significantly extend progression-free survival, and improve quality of life through reducing the lines of chemotherapy a patient needs to undergo. The PBAC noted that this advice was supportive of the evidence provided in the submission.

### ***Consumer meeting with Ovarian Cancer Australia***

- 6.4 This meeting was held between Ovarian Cancer Australia and representatives of the PBAC prior to the PBAC consideration of olaparib. The following points provide a summary of the discussion:
- The condition adversely impacts on the quality of life for patients and their families, which includes effects on social, economic and psychological wellbeing. Patients are aware that recurrence of the disease following initial treatment is inevitable. With few new drugs becoming available in recent years, chemotherapy offered at the point of recurrence is less effective than that given on initial diagnosis.
  - Whilst it was acknowledged that olaparib treatment is not a cure for ovarian cancer, it was perceived as an important advance – it was considered to delay disease recurrence while preserving a good quality of life. It was hoped that better understanding of ovarian cancer has resulted in more effective treatments, allowing patients to delay exposure to the detrimental effects of cytotoxic chemotherapy.
  - Without PBS subsidy access, the cost of olaparib would prohibit most patients from accessing the drug. For many women diagnosed with ovarian cancer, it is at a time when they are no longer working fulltime and are therefore limited in their ability to fund the treatment themselves.
  - Patient perspectives of olaparib are that the adverse events (most commonly fatigue) are less than those experienced when receiving

chemotherapy. For many women, the adverse effects of chemotherapy prevent them from remaining in the workforce.

### Clinical trials

**Table 1: Clinical evidence presented by submission for drug**

			<b>Overall risk of bias in clinical trials</b>	
Retrospective test-stratified randomised controlled trial of drug vs usual care <sup>a</sup>	<input checked="" type="checkbox"/>	k=1	n=265	Unclear risk of bias. BRCAm subgroup might not be appropriate due to missing data with BRCAwt/unknown subgroups.

Source: compiled during evaluation

BRCAm = BRCA1 or BRCA2 mutation; BRCAwt = BRCA wildtype; k = number of studies; n = number of study participants

<sup>a</sup> population is randomised to proposed drug or comparator and then biomarker status determined by testing in some or all of the trial population.

6.5 Details of the pivotal trial presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
<b>Direct</b>	<b>randomised trial</b>	
Study 19	Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens.  Ledermann J, Harter P, Gourley C, <i>et al.</i> Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.  Ledermann J, Harter P, Gourley C, <i>et al.</i> Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCAm status in a randomised phase 2 trial.  Matulonis UA, Harter P, Gourley C, <i>et al.</i> Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer and a BRCA mutation: Overall survival adjusted for post-progression PARP inhibitor therapy.	Clinical study report (CSR). 31 July 2013  NEJM. 2012; 366(15):1382-1392.  The Lancet Oncol. 2014; 15(8):852-861.  Gynecologic Oncology. 2015; 137:8.

Source: Table BD.3, pp41-42 of the submission

- 6.6 The key features of Study 19 are summarised in Table 3.

**Table 3: Key features of direct randomised controlled trial (Study 19)**

N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
265	ITT, R, DB, 37.3month follow-up (med)	Unclear	PSR ovarian cancer	PFS, OS	No
136	Non-stratified subgroup analysis	Unclear	PSR ovarian cancer, <i>BRCAM</i>	PFS, OS	Yes, for PFS
97	<i>Post hoc</i> <sup>a</sup> subgroup analysis	Unclear	PSR ovarian cancer, <i>BRCAM</i>	PFS, OS	Yes, for OS

Source: compiled during the evaluation

*BRCAM* = *BRCA1* or *BRCA2* mutation; DB = double blind; ITT = intention-to-treat; OS = overall survival; PARP = polyadenosine 5' diphosphoribose polymerase; PFS = progression-free survival; PSR = platinum-sensitive relapsed; R = randomised; med = median; m = month

<sup>a</sup> Removed all patients from treatment centres where at least one patient was allowed to crossover to receive post-progression treatment with a PARP inhibitor

- 6.7 Study 19 was a randomised, double-blind Phase II trial that compared olaparib maintenance monotherapy with placebo in women with platinum-sensitive relapsed ovarian cancer (n=265). Patients were stratified by: interval between disease progression and completion of platinum-based chemotherapy; objective response to platinum-based chemotherapy; and ethnic descent (Jewish vs. non Jewish). Of these, 136 patients were found to have a *BRCAM* (with testing conducted retrospectively). A total of 14 patients (23%) of this subgroup randomised to placebo were allowed to crossover to received a PARP inhibitor (including olaparib) after disease progression, as decided by the investigator. As a result, the submission used a *post hoc* analysis (Matulonis, 2015) which removed all patients from treatment centres where at least one patient was allowed to crossover to receive post-progression treatment with a PARP inhibitor ('PARPi sites-excluded method'). As a sensitivity analysis, the rank preserving structural failure time (RPSFT) was also used; however, confidence intervals around the resulting point estimates were not provided.
- 6.8 The trial population in Study 19 was broader than the proposed PBS restriction for olaparib; they included patients without *BRCAM* (i.e. *BRCA* wild type[wt]/unknown). However, this allowed a comparison of the extent of olaparib treatment effects across these two key patient subgroups.
- 6.9 The risk of bias was unclear for the ITT population and *BRCAM* subgroup of Study 19. While the trial was double-blind, the primary outcome (progression-free survival) was a surrogate outcome. As the adverse event profile for patients on olaparib differed from those on placebo, the investigator and patients might have known the treatment. Although *BRCAM* was a prespecified subgroup, the study was not stratified for *BRCAM* at randomisation. Therefore, it was unclear if the *BRCAM* subgroup was appropriate. Further, there was significant heterogeneity across *BRCAM* testing methods which could introduce bias of unknown direction. The PSCR (page 4) claimed that it was impractical to initiate *BRCAM* testing for a large number of women for the purposes of stratification. Instead, Study 19 was stratified for Jewish vs non-Jewish ethnic descent as *BRCAM* are known to occur more frequently in people with Ashkenazi Jewish heritage.

**Comparative effectiveness**

- 6.10 Results of the primary outcome, progression-free survival (as assessed by the investigator using Response Evaluation Criteria in Solid Tumours (RECIST) criteria) for Study 19 are presented in Table 4.

**Table 4: Progression-free survival results and Kaplan-Meier estimates for Study 19<sup>a</sup>**

Population	Overall pop. (ITT)		BRCAm subgroup		BRCAwt /unknown <sup>b</sup>	
	Olaparib (n=136)	Placebo (n=129)	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=57)	Placebo (n=61)
Med duration of Tx	259 days	139 days	329 days	139 days	—	—
Events n/N (%)	60/136 (56.6%)	93/129 (72.1%)	26/74 (35%)	46/62 (74%)	32/57 (49%)	44/61 (75%)
RECIST PFS	59/136 (43.4%)	93/129 (72.1%)	—	—	—	—
Deaths	1/136 (0.7%)	0/129 (0%)	—	—	—	—
Median PFS; mths (95% CI)	8.4 (7.4, 11.5)	4.8 (4.0, 5.5)	11.2 (8.3, NC)	4.3 (3.0, 5.4)	7.4 (5.5, 10.3)	5.5 (3.7, 5.6)
HR (95% CI)	<b>0.35 (0.25, 0.49)</b>		<b>0.18 (0.10, 0.31)</b>		<b>0.54 (0.34, 0.85)</b>	

Source: Table BD.19, p75 of the submission; Table 54, p194 of the CSR; Figure 2, p855 of Ledermann (2014); and extracted from Table 11.2.1.1.c, p1592 of the CSR

BRCAm = BRCA1 or BRCA2 mutation; BRCAwt = BRCA wildtype; CI = confidence interval; CSR = clinical study report; HR = hazard ratio; ITT = intention-to-treat; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; med = median; mths = months; pop = population; Tx = treatment; **bold** = statistically significant

<sup>a</sup> The submission used the values for hazard ratios from Ledermann (2014) for the economic model (differences due to rounding)

<sup>b</sup> Extracted from Ledermann (2014)

- 6.11 At the primary analysis of Study 19 (median follow-up 37.3 months), olaparib showed statistically significant superior progression-free survival compared with placebo in the ITT population (hazard ratio (HR): 0.35; 95% confidence interval (CI): 0.25 to 0.49); BRCAm subgroup (HR: 0.18; 95% CI: 0.11 to 0.31); and BRCAwt/BRCA unknown subgroup (HR: 0.53; 95% CI: 0.33 to 0.84). The ESCs noted that, in Study 19, BRCAwt/BRCA unknown status predicted a reduced extent of improvement in progression-free survival. The ESCs further requested that a statistical test of interaction be presented for the treatment effect variation of the PFS hazard ratios across the BRCAm and BRCAwt/BRCA unknown subgroups from Study 19.
- 6.12 These results might not be generalisable to Australian clinical practice, which uses cancer antigen 125 (CA-125) as a measure of progression (not RECIST criteria as per Study 19). The ESCs noted the PSCR claim (page 5) that, in Study 19, clinicians were given the option to continue their patients on maintenance therapy, even if there was RECIST progression, if they considered the patient was still benefiting from the blinded study treatment. The ESCs considered that likely Australian practice would be to monitor less intensively for progression than in Study 19, and to continue olaparib therapy if there is any equivocation about whether progression had occurred. For both these reasons, the duration of olaparib therapy is likely to be longer in real-world Australian practice than that estimated from Study 19.
- 6.13 For progression-free survival in the economic model, the submission used the hazard ratio for patients classified with a BRCA mutation (0.18 (95% CI: 0.11 to 0.32)), and the hazard ratio for patients classified without a mutation

*BRCAwt/unknown* (0.54, (95% CI: 0.34 to 0.86)) from Study 19. This was appropriate.

- 6.14 The results for overall survival from Study 19 are summarised in Table 5 and Figure 1.

**Table 5: Overall survival results and Kaplan-Meier estimates for Study 19<sup>a</sup>**

Population	Overall pop. (ITT)		BRCAm subgroup		BRCAwt /unknown <sup>b</sup>	
	Olaparib (n=136)	Placebo (n=129)	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=57)	Placebo (n=61)
Drug						
Sample size						
Med duration of Tx	259 days	139 days	329 days	139 days	—	—
Deaths n/N (%)	77/136 (56.6%)	77/129 (59.7%)	37/74 (50%)	34/62 (55%)	36/57 (63%)	41/61 (67%)
Median OS; mths (95% CI)	29.8 (27.2, 35.7)	27.8 (24.4, 34.0)	34.9 (29.2, NC) <sup>b</sup>	31.9 (23.1, 40.7) <sup>b</sup>	24.5 (19.8, 35.0)	26.2 (22.6, 33.7)
Crossover n/N (%)	0/136 (0%)	16/129 (12.4%)	0/74 (0%)	14/62 (23%)	0/57 (0%)	2/61 (3%)
HR (95% CI)	0.88 (0.64, 1.21)		0.73 (0.45, 1.17)		0.99 (0.63, 1.55)	

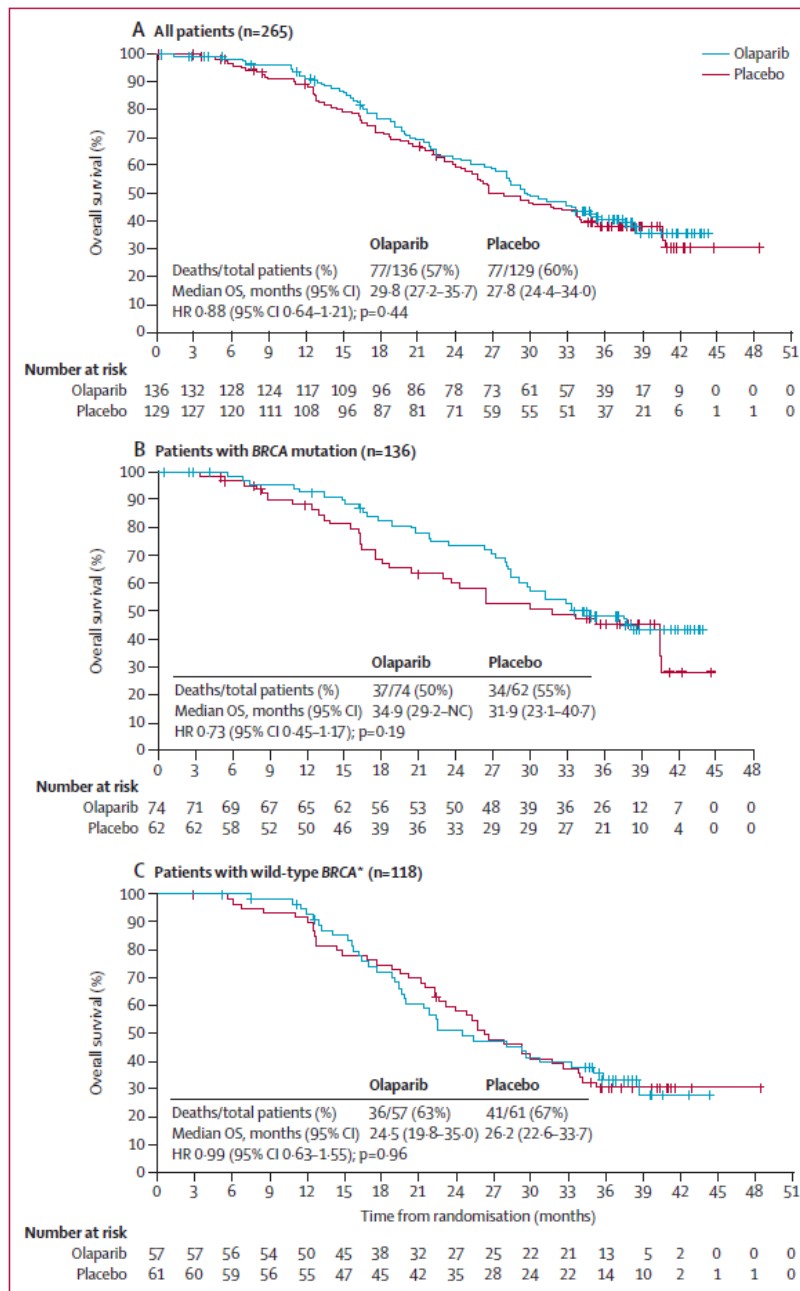
Source: Table BD.20, p78 of the submission; Table 60 p204; Table 11.2.2.1.c, p1603 of the CSR

*BRCAm* = *BRCA1* or *BRCA2* mutation; *BRCAwt* = *BRCA* wildtype; CI = confidence interval; CSR = clinical study report; HR = hazard ratio; ITT = intention-to-treat; NC = not calculable; OS = overall survival; med = median; mths = months; pop = population; Tx = treatment

<sup>a</sup> The submission used the values for hazard ratios from Ledermann (2014), rather than estimates from the CSR

<sup>b</sup> Extracted from Ledermann (2014)

Figure 1: Kaplan-Meier curves for OS in Study 19



Source: Figure 3, p856 of Ledermann (2014)

CI = confidence interval; HR = hazard ratio; NC = not calculable; OS = overall survival

\* Wild-type BRCA included patients with no known BRCA mutation and those with a BRCA mutation of unknown significance

- 6.15 At the interim analysis of overall survival (median follow-up 37.3 months), there was no statistically significant benefit from olaparib in the ITT population, or the two subgroups according to BRCAm status.
- 6.16 At this interim analysis, the Kaplan-Meier curves for both the ITT population and the BRCAm subgroup showed convergence of benefit at approximately 33 months; however, there was crossover to olaparib in the placebo arm that could bias against olaparib. This was relatively more pronounced in the

*BRC*Am subgroup (23%) than in the *BRC*Awt/unknown subgroup (3%). For this reason, the submission used the estimates of survival benefit from the *post hoc* analysis (*BRC*Am subgroup with ‘PARPi sites excluded method’), and presented the results for the RPSFT method (Table 6).

**Table 6: OS results from Study 19 and *post hoc* analyses that adjust for crossover**

Analysis	Study 19		Post hoc Matulonis (2015)		Post hoc <sup>a</sup>		
	<i>BRC</i> Am subgroup		<i>BRC</i> Am subgroup ‘PARPi sites-excluded method’		<i>BRC</i> Am subgroup RPSFT method		
Drug Sample size	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=57)	Placebo (n=40)	$\beta_1$	$\beta_2$	$\beta_3$
Med Tx duration	329 days	139 days	—	—	—	—	—
Events n/N (%)	37/74 (50%)	34/62 (55%)	28/57 (49%)	22/40 (55%)	—	—	—
Med OS mths (95% CI)	34.9 (29.2, NC <sup>b</sup> )	31.9 (23.1, 40.7 <sup>b</sup> )	34.9 (NR)	26.6 (NR)	—	—	—
Acceleration factor <sup>d</sup>	—	—	—	—	3.21 <sup>d</sup>	3.22 <sup>d</sup>	5.00 <sup>d</sup>
HR (95% CI)	0.73 (0.45, 1.17) <sup>c</sup>		<b>0.52 (0.28, 0.97)</b>		0.664 <sup>e</sup>	0.664 <sup>e</sup>	0.654 <sup>e</sup>

Source: Table BD.20, p78; Table C.7, p173 of the submission; Table 60 p204 of the CSR, of the submission  
*BRC*Am = *BRCA1* or *BRCA2* mutation; CI = confidence interval; CSR = clinical study report; HR = hazard ratio; NR = not reported; OS = overall survival; PARPi = polyadenosine 5’ diphosphoribose polymerase inhibitor; RPSFT = rank preserving structural failure time; med = median; mths = months; Tx = treatment;  $\beta$  = acceleration factor; **bold** = statistically significant;

<sup>a</sup> The submission presented three comparisons of three different acceleration factors that approximated a 34-35% reduction in hazard of death

<sup>b</sup> Extracted from Ledermann (2014)

<sup>c</sup> The submission used the values from Ledermann 2014

<sup>d</sup> The acceleration factor value was used to divide the duration of survival after crossover to estimate the survival if the patients would not have crossed over.

<sup>e</sup> The submission did not provide a 95% CI for the RPSFT hazard ratio point estimates

- 6.17 Using the *post hoc* ‘PARPi sites-excluded method’ for this interim analysis resulted in a statistically significant improvement in overall survival for olaparib versus placebo in patients with the *BRCA* mutation (HR: 0.52; 95% CI: 0.28 to 0.97). For patients with a *BRC*Awt/unknown, no improvement in overall survival was observed (HR: 0.98; 95% CI: 0.59 to 1.64).
- 6.18 The PSCR (Table 1) presented updated survival data from Study 19, which reported a statistically significant increase in overall survival in both the *BRC*Am ITT population and the *BRC*Am post-hoc sites excluded population. The results are summarised in Table 7. The ESCs noted the updated survival data and considered that the two sets of Kaplan-Meier curves reflecting these updated results would be highly informative, alongside an update of the corresponding OS results for the overall (ITT) Study 19 population, the *BCRA*wt/unknown subgroup, and a statistical test of interaction for the treatment effect variation of the updated overall survival hazard ratios across the *BRC*Am and *BRC*Awt/*BRCA* unknown subgroups from Study 19.

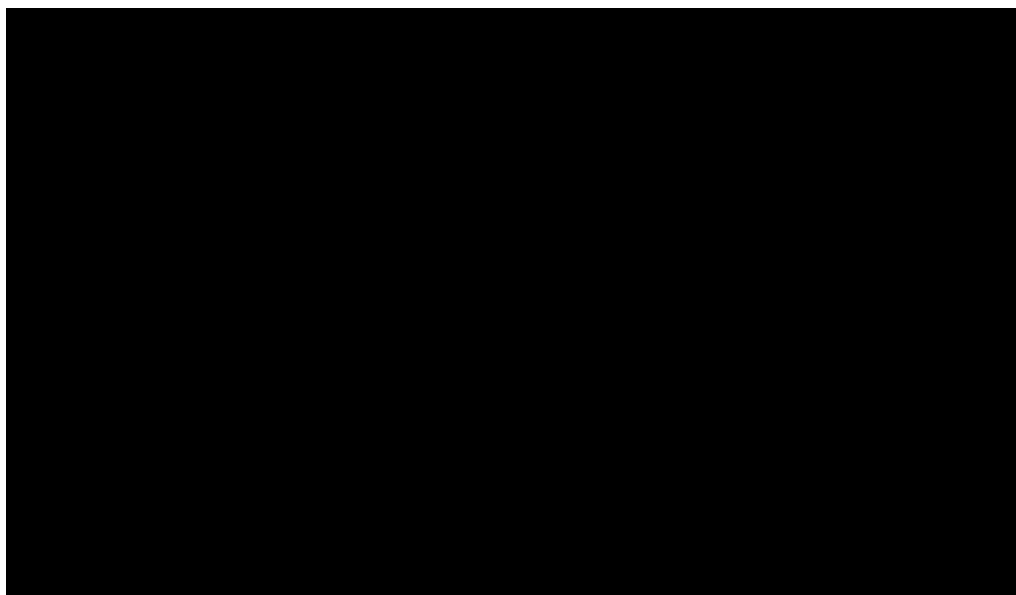
Table 7: Updated overall survival results in BRCAm subgroups

Population/ Treatment group	Events n/N (%)	Median, months	HR	(95% CI)	Nominal p- value
<b>BRCAm population (N=136)</b>					
Olaparib	█ (█%)	█	█	(█, █)	█
Placebo	█ (█%)	█	█	█	█
<b>BRCAm population, PARPi sites-excluded (N=96)</b>					
Olaparib	█ (█%)	█	█	(█, █)	█

Source: Pre-Sub-Committee Response p. 11

- 6.19 The Pre-PBAC response provided unpublished preliminary Kaplan-Meier curves for the updated OS analyses; these are presented in the table below.

Figure 2: Preliminary Kaplan Meier curves for the updated OS analyses



Source: Figure 1, Pre-PBAC Response Attachment 1

- 6.20 For overall survival in the economic model, the submission used the hazard ratio for patients classified with a *BRCA* mutation of the *post hoc* analysis for *BRCAm* subgroup with ‘PARPi sites-excluded method’ 0.52 (95% CI: 0.28 to 0.96) from Matulonis (2015). For patients classified as without a mutation, the submission used the hazard ratio for *BRCAwt/unknown* 0.98 (95% CI: 0.59 to 1.64) from Ledermann (2014). In a sensitivity analysis, the RPSFT methodology was used. The submission used an acceleration factor ranging from 3.2 to 5.0, meaning that every 3.2 to 5 months of reported survival time in the placebo arm post switching would be adjusted down to 1 month. This resulted in an adjusted hazard ratio of 0.67 to 0.66, respectively. The submission did not provide estimates of variance around the RPSFT point estimates.

**Comparative harms and extended assessment of comparative harms**

- 6.21 The adverse events for the ITT population and the *BRCAM* subgroup are presented in Table 8.

**Table 8: Summary of key adverse events in Study 19 (≥ 1 AE in any category) (SAS <sup>a</sup>)**

Any AE category <sup>b</sup> n (%)	Overall population		<i>BRCAM</i> subgroup	
	Olaparib (n=136)	Placebo (n=128)	Olaparib (n=74)	Placebo (n=62)
Drug Sample size				
Median duration of treatment	259 days (~8.6m)	139 days (~4.6m)	329 days (~11.0m)	139 days (~4.6m)
Dose adherence; mean (SD)	84.4% (24)	96.6% (10)	83% (25)	97% (11)
AE	132 (97.1%)	119 (93.0%)	72 (97%)	58 (94%)
TR-AE <sup>c,d</sup>	122 (89.7%)	93 (72.7%)	67 (91%)	45 (73%)
AE of CTCAE > Grade 3 <sup>c,d</sup>	56 (41.2%)	28 (21.9%)	29 (39%)	11 (18%)
TR-AE of CTCAE > Grade 3 <sup>c</sup>	34 (25.0%)	10 (7.8%)	16 (22%)	5 (8%)
Any TR-AE that led to death	1 (0.7%)	0 (0%)	1 (1%)	0 (0%)
Any SAE	25 (18.4%)	11 (8.6%)	16 (22%)	6 (10%)
TR-SAE <sup>c</sup>	8 (5.9%)	1 (0.8%)	5 (7%)	1 (2%)
AE led to discontinuation	6 (4.4%)	2 (1.6%)	5 (7%)	0 (0%)

Source: Table BD.22, p89 of the submission; Table 39, p141 of the CSR

AE = adverse events; *BRCAM* = *BRCA1* or *BRCA2* mutation; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event; SAS = safety analysis set; SD = standard deviation; TR = treatment-related; m = months

<sup>a</sup> Safety analysis set had 1 less patient in the placebo arm; 3 patients received incorrect study treatment due to dispensing error

<sup>b</sup> Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each category.

<sup>c</sup> Investigator assessed

<sup>d</sup> The submission included AEs that led to death as Grade 3 or higher (explains the difference in these estimates with CSR).

- 6.22 The submission stated the safety profile of olaparib was similar between patients with *BRCAM* and the ITT population, with adverse events reported in 91% of the olaparib group versus 73% of the placebo group, and Grade 3 or higher adverse events reported in 39% of the olaparib group versus 18% of the placebo group; the latter was statistically significant. Olaparib was associated with more treatment-related adverse events, serious adverse events and treatment-related serious adverse events. The submission stated that these were mild to moderate and did not require discontinuation of therapy.
- 6.23 The most common Grade 3+ (≥ 3%) adverse events for olaparib were fatigue, anaemia and neutropenia, while placebo treatment did not result in any Grade 3+ adverse events in more than 3% of the patients. For the economic model, the submission used the Grade 3+ (≥ 2%) adverse events.
- 6.24 The Periodic Benefit-Risk Evaluation Report has identified the following important risks associated with olaparib: anaemia, thrombocytopenia, neutropenia, raised creatinine levels and nausea-induced vomiting. The important potential risks are myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), new primary malignancies, pneumonitis and potential for off-label use. The ESCs were particularly concerned about the long term safety of olaparib therapy, noting the emerging association between

olaparib and the development of MDS and AML. The Clinical Evaluation Report stated that it is plausible that an agent blocking DNA repair would increase the risk of deleterious mutations causing transformation to a malignant phenotype, especially during or following chemotherapy with DNA-damaging agents or radiation therapy. The ESCs further warned that the biological rationale for targeting olaparib to BRCAm patients for better ovarian cancer outcomes provides the same basis for expecting that these adverse effects will be more prevalent in BRCAm patients than in BRCAwt patients. The Pre-PBAC response (page 2) argued that MDS and AML are recognised side effects of conventional chemotherapy, noting that all olaparib patients reporting MDS/AML had also received extensive treatment with DNA damaging agents including platinum. The response further noted that the reported incidence for ovarian cancer patients definitely known to have received olaparib is 0.78%, which is lower than the reported incidence of MDS/AML in ovarian cancer patients who did not receive olaparib (1.3%).

### Benefits/harms

6.25 A summary of the comparative benefits and harms for olaparib versus placebo for the whole trial population of Study 19 is presented in Table 9.

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

<b>BENEFITS</b>						
<b>Interim analysis: Study 19 ITT (n=265)</b>						
<b>PFS</b>						
	<b>Olaparib</b>	<b>Placebo</b>	<b>Absolute diff.</b>	<b>HR (95% CI)</b>		
Progressed disease; n/N (%)	60/136 (56.6%)	93/129 (59.7%)	—	<b>0.35 (0.25, 0.49)</b>		
Median; months	8.4 (7.4, 11.5)	4.8 (4.0, 5.5)	—	—		
<b>OS<sup>a</sup></b>	—	—	—	—		
Died; n/N (%)	77/136 (56.6%)	77/129 (59.7%)	—	0.88 (0.64, 1.21)		
Median; months	29.8 (27.2, 35.7)	27.8 (24.4, 34.0)	—	—		
<b>Harms - Grade 3/4</b>						
				<b>Event rate/100 patients<sup>b</sup></b>		
	<b>Olaparib</b>	<b>Placebo</b>	<b>RR (95% CI)</b>	<b>Olaparib</b>	<b>Placebo</b>	<b>RD (95% CI)</b>
Fatigue; n/N	10/136	4/128	—	7.4	3.1	—
Anaemia; n/N	7/136	1/128	—	5.1	0.8	—
Neutropenia n/N	5/136	1/128	—	3.7	0.8	—

Source: Table BD.19, p75 of the submission, Table 54, p194; Figure 2, p855 of Ledermann (2014); and extracted from Table 11.2.1.1.c, p1592 of the CSR

BRCAm = BRCA1 or BRCA2 mutation; CI = confidence interval; CSR = clinical study report; HR = hazard ratio; ITT = intention-to-treat; NC = not calculable; OS = overall survival; PARP = polyadenosine 5' diphosphoribose polymerase; PFS = progression-free survival; RD = risk difference; RR = relative risk; diff = difference; **bold** = statistically significant

<sup>a</sup> 16 (12%) patients were allowed to crossover from placebo to receive a PARP inhibitor, post-progression

<sup>b</sup> Median duration of follow-up 37.3 months

6.26 In the ITT population of Study 19, median progression-free survival and overall survival for women on olaparib were approximately 8.4 months and 29.8 months, respectively; whereas median progression-free survival and overall survival for women on placebo were 4.8 months and 27.8 months, respectively.

- 6.27 On the basis of the direct comparison presented by the submission (ITT), for every 100 patients treated with olaparib in comparison with placebo over a 37.3 months median duration of follow-up, there were:
- approximately four additional Grade 3 or higher cases of fatigue;
  - approximately four additional Grade 3 or higher cases of anaemia; and
  - approximately three additional Grade 3 or higher cases of neutropenia.
- 6.28 A summary of the comparative benefits and harms for olaparib versus placebo for the *BRCAM* subgroup of Study 19 is presented in Table 10.

**Table 10: Summary of comparative benefits and harms for olaparib and placebo: *BRCAM***

<b>BENEFITS</b>						
<b>Interim analysis: Study 19 subgroup (n=136)</b>						
<b>PFS</b>						
	<b>Olaparib</b>	<b>Placebo</b>	<b>Absolute diff.</b>	<b>HR (95% CI)</b>		
Progressed disease; n/N (%)	26/74 (35%)	46/62 (74%)	—	<b>0.18 (0.10, 0.31)</b>		
Median; months	11.2 (8.3-NC)	4.3 (3.0-5.4)	—	—		
<b>OS: crossover censored</b> <sup>a,b</sup>	—	—	—	—		
Died; n/N (%)	37/74 (50%)	34/62 (55%)	—	0.73 (0.45,1.17)		
Median; months	34.9 (29.2, NC)	31.9 (23.1, 40.7)	—	—		
<b>Harms - Grade 3/4</b>						
				<b>Event rate/100</b>	<b>patients <sup>b</sup></b>	
	<b>Olaparib</b>	<b>Placebo</b>	<b>RR (95% CI)</b>	<b>Olaparib</b>	<b>Placebo</b>	<b>RD (95% CI)</b>
Fatigue; n/N	5/74	1/62	—	7	2	—
Anaemia; n/N	4/74	1/62	—	5	2	—
Neutropenia n/N	3/74	1/62	—	4	2	—

Source: Table BD.19, p75 of the submission, Table 54, p194; Figure 2, p855 of Ledermann (2014); and extracted from Table 11.2.1.1.c, p1592 of the CSR

*BRCAM* = *BRCA1* or *BRCA2* mutation; CI = confidence interval; CSR = clinical study report; HR = hazard ratio; NC = not calculable; NR = not reported; OS = overall survival; PARP = polyadenosine 5' diphosphoribose polymerase; PFS = progression-free survival; RD = risk difference; RR = relative risk; diff = difference; **bold** = statistically significant

<sup>a</sup> 14 (23%) patients were allowed to crossover from placebo to receive a PARP inhibitor, post-progression

<sup>b</sup> Median duration of follow-up 37.3 months

- 6.29 In the *BRCAM* subgroup of Study 19, median progression-free survival and overall survival for women on olaparib were approximately 11.2 months and 34.9 months, respectively; whereas median progression-free survival and overall survival for women on placebo were 4.3 months and 31.9 months, respectively.
- 6.30 On the basis of the direct comparison presented by the submission (*BRCAM* subgroup), for every 100 patients treated with olaparib in comparison with placebo, over a 37.3 months median duration of follow-up, there were:
- approximately five additional Grade 3 or higher cases of fatigue;
  - approximately three additional Grade 3 or higher cases of anaemia; and
  - approximately two additional Grade 3 or higher cases of neutropenia.
- 6.31 The ESCs considered that, although the benefits and harms comparison appeared to favour olaparib, it did not take into account the long-term implications of olaparib treatment, including the predictable development of MDS and AML in *BRCAM* patients.

### **Clinical claim**

- 6.32 The submission described olaparib as superior in terms of comparative effectiveness and as “consistent and well characterised” in terms of comparative safety over standard follow-up care (placebo) in patients with platinum-sensitive resistant ovarian cancer with the *BRCA* mutation.
- This claim of superior comparative effectiveness of olaparib over placebo was shown by the data for progression-free survival. Olaparib treatment in patients with platinum-sensitive relapsed ovarian cancer resulted in a statistically significant improvement in progression-free survival. However, this was not reflected in a significant improvement in overall survival (all patients, patients with *BRCAM*, or patients with *BRCAwt/unknown*). The ESCs noted the PSCR included updated data from Study 19, which demonstrated a significant improvement in overall survival for *BRCAM* patients, and considered this was informative;
  - *BRCAM* status, which was claimed to be prespecified, was not stratified for at randomisation. The submission used this prespecified non-stratified subgroup to claim that olaparib has superior efficacy with regards to progression-free survival compared with placebo treatment in patients with the *BRCA* mutation. *BRCA* status was measured retrospectively for many patients within Study 19. As there were missing *BRCAM* data for the *BRCAwt/unknown* subgroup, it was unclear if potential confounding could exist for these outcomes measured. The PSCR (page 4) claimed that data was only missing for 11 out of 265 patients (4%), however the ESCs noted that 108 participants (41%) had either missing or unknown test results when broken down by type of testing (tumour or germline), which affects interpretation of the data for the purposes of assessing the requested *BRCA* testing strategy. The Pre-PBAC response (page 2) disagreed with the ESCs interpretation, stating that it was not an accurate reflection of the total missing data because patients received both germline and tumour testing where possible. The response also noted that *BRCA* status was determined for 254 of the 265 Study 19 participants (96%) through either germline or somatic testing; and
  - the submission used the estimates from a further post hoc subgroup analysis, which removed all data from the study sites where patient crossover occurred, to estimate the overall survival without confounding; however, this process resulted in a total of 71% of the *BRCAM* data (including patients who did not crossover) from the analysis, which represents a bias of unknown direction. The PSCR (page 6) argued that the validity of the “PARPi sites excluded method” was dependent on the subgroup including sufficient patients, being unbiased, and having comparable treatment arms in terms of potential confounders, and stated that all three of these criteria were met. The PSCR (page 7) claimed that as there were no statistically significant differences in any measured parameter, it was less likely that the “PARPi sites excluded method” introduced bias of unknown direction and magnitude. The ESCs noted that the “PARPi sites excluded method” was unorthodox and not previously accepted by the PBAC in addressing the issue of crossover. The ESCs advised that removing all patients in a centre where crossover occurred would clearly have the effect of reducing precision, whilst the effect on bias remains unclear. The ESCs also noted that a comparison

was made with one of the more widely used statistical adjustment methods, the rank-preserving structural failure time (RPSFT) model, but advised that this was limited because the confidence interval around each reported point estimate was also required. The Pre-PBAC response reiterated that the sites excluded analysis was a valid approach, stating that the updated ratio for OS in the 'sites excluded' subgroup (HR: 0.49; 95% CI: 0.28 to 0.86) was consistent with the updated supplementary RPSFT analysis (HR: 0.58), with the point estimate used in the original model (HR: 0.52) falling between the two updated estimates.

- 6.33 The claim of “consistent and well characterised safety profile” was interpreted during the evaluation as olaparib having an inferior but acceptable safety profile. A conclusion of inferior safety profile might be reasonable, but would have the following limitations:
- the short median duration of treatment (37.3 months). The ESCs considered that this timeframe was too short in the context of longer term safety concerns regarding the development of MDS and AML;
  - the duration of treatment might not reflect clinical practice as patients continue treatment until disease progression or toxicity;
  - the amount of missing data was high due to censoring; and
  - the absence of safety data for patients with *BRC*Awt/unknown. The ESCs considered that this may favour olaparib, as *BRC*Awt patients may be at less risk of developing MDS and AML.
- 6.34 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.35 The PBAC considered that the claim of inferior comparative safety was reasonable.

#### **Claim of co-dependence**

- 6.36 The submission claimed the co-dependent technologies ‘*BRCA* testing and olaparib’ to be superior to ‘No *BRCA* testing and standard follow-up care’.
- 6.37 The submission did not provide a detailed comparison of these two scenarios, rather it focussed on the comparison of the effectiveness of olaparib in patients with *BRC*Am. The claim of co-dependence between the technologies of *BRCA* testing and olaparib relies on an acceptance that *BRCA* testing predicts an important variation between *BRC*Am and *BRC*Awt patients in the effectiveness of olaparib, and that this is distinguishable from the prognostic value of *BRCA* testing. This claim might not be reasonable in the Australian setting as the key issues were:
- The sensitivity and specificity of the germline and tumour *BRCA* testing might be lower than 100% in the Australian setting:
    - If the specificity is less than 100%, olaparib treatment might be less effective with regards to progression-free survival, as the efficacy was lower in patients with *BRC*Awt/unknown.
    - If the sensitivity is less than 100%, fewer patients with *BRC*Am would be treated, reducing the potential efficacy of the ‘*BRCA* testing and olaparib’ co-dependent technology.

- The ESCs noted that, although the initial Study 19 results provided by the submission did not show that olaparib treatment resulted in significant overall survival in the ITT population or the prespecified *BRCAM* or *BRCAwT/unknown* subgroups, the PSCR (Table 1) provided updated survival data from Study 19 which showed statistically significant improvements in overall survival in the *BRCAM* subgroups.
- The ESCs advised that an informative way to help establish the claim of co-dependence between *BRCA* testing and olaparib would be to present statistical tests of interaction for the treatment effect variations on (a) progression-free survival and (b) updated overall survival hazard ratios across the *BRCAM* and *BRCAwT/unknown* subgroups from Study 19. The Pre-PBAC response (page 2) stated that the PFS benefit observed in the Study 19 *BRCAM* population (HR: 0.18; 95% CI: 0.10 to 0.31) was greater than that observed in the overall population (HR: 0.35; 95% CI: 0.25 to 0.49) and in the *BRCAwT/unknown* population (HR: 0.54; 95% CI: 0.34 to 0.85). The response further stated that the statistical interaction test performed for *BRCAM* status by treatment group was statistically significant ( $p=0.03$ ), and noted that tests for interaction on the OS endpoint were not available.

### **Economic analysis**

- 6.38 The submission presented a modelled economic evaluation (cost-utility analysis) based on the superiority claim of the proposed scenario ('*BRCA* testing and olaparib') over the current scenario ('No *BRCA* testing and standard follow-up care'). The economic model was based on the progression-free survival benefit from a prespecified subgroup analysis of *BRCA* status from Study 19 and the overall survival benefit from a further *post hoc* subgroup analysis of the *BRCAM* subgroup from Study 19 (Matulonis, 2015). However, the economic model appeared to be unreliable, due to poor internal validity with the interim Study 19 trial results.
- 6.39 The modelled evaluation was divided into two phases, testing and treatment. For the testing phase, a simple decision analytic tree was used to determine the proportion of women who would qualify for olaparib treatment on the basis of the underlying prevalence of *BRCA* mutations. Patients who tested positive for *BRCAM* received olaparib maintenance therapy. Patients who tested negative for *BRCA* mutation (*BRCAwT/unknown*) received placebo.
- 6.40 The second part of the model followed on from the testing phase, and consisted of a multi-state Markov model which simulated the progress of disease and longer-term consequences. The model duration was 10 years. A 10-year model might overestimate the survival of women with *BRCAM* platinum-sensitive ovarian cancer and introduced uncertainty, particularly when coupled with the extrapolation of outcomes beyond the observed trial duration.
- 6.41 The PSCR (page 7) argued that Australian and International data provide strong evidence that a substantial number of patients with advanced ovarian cancer remain alive at 10 years, and thus a 10-year time horizon represents a conservative approach with biases against olaparib.

- 6.42 The ESCs considered that a time horizon of 10 years may not be conservative, considering the median progression-free survival in Study 19 was 8.4 months and 4.8 months for women on olaparib and placebo respectively, and the overall survival was 34.9 months and 30.2 months respectively. The ESCs considered that the choice of a 10-year time horizon was likely to bias in favour of olaparib.
- 6.43 There were three health states in the second part of the model: ‘alive, non-progressive disease’, ‘alive, progressive disease’ and ‘dead’. All patients entered the model in the progression-free health state. The PSCR (page 8) acknowledged that the three state model did not explicitly capture subsequent relapses and further chemotherapy, however argued that this was conservative and would have led to under-estimation of the true cost-effectiveness of olaparib. The ESCs considered that this type of three state model was typically used for patients with end-stage malignancy.

**Table 11: Summary of model structure and rationale**

Time horizon	10 years in the model base case vs. a median follow-up of 37.3 months
Outcomes	QALY <sup>a</sup> and YoLG
Methods used to generate results	Trial-based; Markov model; cohort expected value analysis; deterministic sensitivity analysis
Cycle length	28 days
Transition probabilities	Based on Kaplan-Meier curves for PFS and OS and extrapolation (log-logistic) of these curves.

Source: constructed during the evaluation

EQ-5D = Euroqol five-dimension tool; FACT-O = Functional Assessment of Cancer Therapy – Ovarian; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; YoLG = years of life gained

<sup>a</sup> Utility values were obtained by mapping the FACT-O scores from Study 19 to the EQ-5D (*UK weights*)

- 6.44 The submission used the underlying prevalence of *BRCAm* of 53.5% in Study 19. In the ‘*BRCA* testing’ arm, the sensitivity and specificity were assumed to be 100%, which meant that the chance of a false negative among women with *BRCAm* was zero, as was the chance of a false positive among women with *BRCAw*t/unknown. Therefore for the base-case model, the submission assumed no adverse consequences of testing. The ESCs noted that the model was relatively insensitive to varying the test accuracy (with test sensitivity varied between 80% and 100% and also with test specificity varied between 80% and 100%).
- 6.45 Patients who remained progression-free were assumed to receive treatment during time in this health state until the mean duration of treatment was reached for olaparib in Study 19. This equated to a maximum of 16.3 months (18 cycles) in the model. However, this did not reflect the proposed restriction as patients can continue treatment until disease progression or toxicity. During the evaluation, an additional sensitivity analysis included continued olaparib treatment costs in all treated patients without disease progression.
- 6.46 The PSCR (page 7) presented a distribution of time on olaparib based on the updated overall survival data, and claimed that it was appropriate to assume that treatment duration would be the same as the mean treatment duration observed in Study 19, because efficacy measures were drawn from an intention-to-treat analysis of Study 19 data. The ESCs noted that the updated data showed an [redacted] in truncated mean treatment duration from [redacted] to

approximately [redacted] days and considered it may be reasonable to expect patients would remain on treatment [redacted] than the truncated mean treatment duration observed in Study 19 to date. The ESCs also noted that, as the time on treatment increased, the estimated incremental cost-effectiveness ratio increased, which suggested that although incremental survival may also have increased, it did so to a lesser extent than the incremental costs. The Pre-PBAC response (page 1 and 5) suggested that uncertainty around mean treatment duration and the corresponding drug costs could be managed through a risk sharing arrangement.

**Table 12: Distribution of patient time on olaparib**

	Number of patients (%)	
	Olaparib	Placebo
Number of treated patients	[redacted]	[redacted]
≥ 1 year	[redacted]	[redacted]
≥ 2 years	[redacted]	[redacted]
≥ 3 years	[redacted]	[redacted]
≥ 4 years	[redacted]	[redacted]
≥ 5 years	[redacted]	[redacted]
≥ 6 years	[redacted]	[redacted]
≥ 7 years	[redacted]	[redacted]

Source: Pre-Sub-Committee Response p. 11

- 6.47 The model presented in the submission was not structurally sound, due to the inappropriate extrapolation method used to construct the transition probabilities, which resulted in substantial mismatching of the overall survival from the interim analysis of Study 19 (Table 13 and Figures 2 and 3).

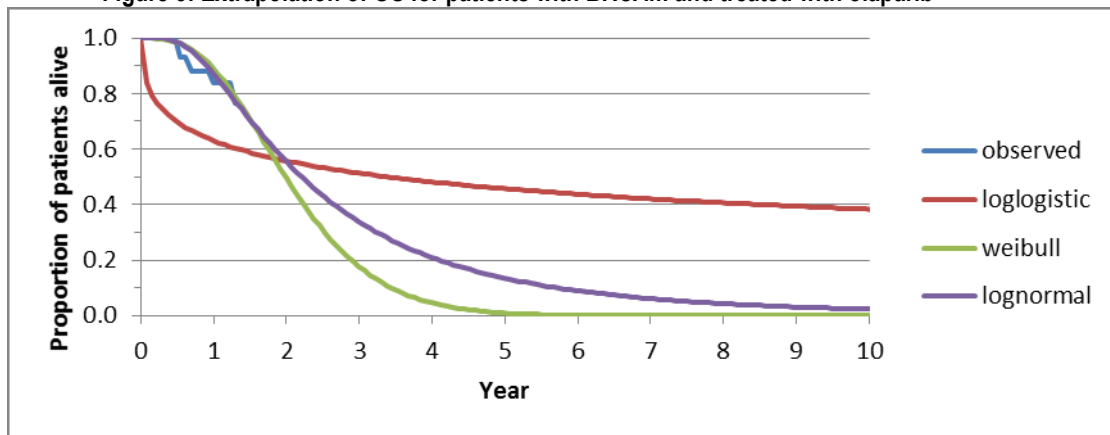
**Table 13: Comparison of median overall survival of model versus Study 19, by BRCAm status**

	Study 19 BRCA+ PARPi	Log logistic
Olaparib	34.9 months	40.5 months
Placebo BRCAm	31.9 months	4.0 months
Placebo BRCAwt/unknown	26.2 months	26.7 months

Source: compiled during evaluation; Excel spreadsheet, Table BD.20, p78 of the submission

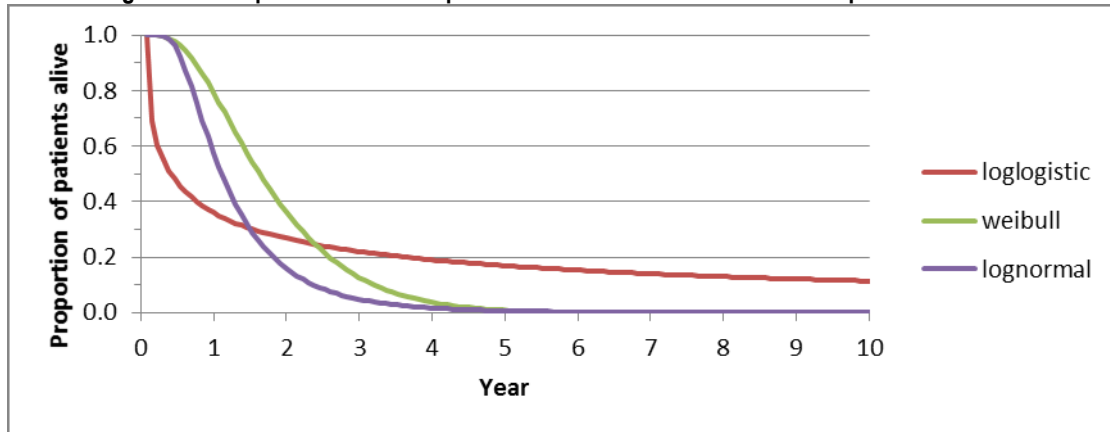
BRCAm = BRCA1 or BRCA2 mutation; BRCAwt = BRCA wildtype; OS = overall survival; PARPi = polyadenosine 5' diphosphoribose polymerase inhibitor

Figure 3: Extrapolation of OS for patients with *BRCAm* and treated with olaparib



Source: compiled during evaluation; Excel spreadsheet  
*BRCAm* = BRCA1 or BRCA2 mutation; IPD = individual patient data; OS = overall survival  
 Note: the observed data are the transitional probabilities derived from the model (per cycle from the Study 19 IPD)

Figure 4: Extrapolation of OS for patients with *BRCAm* and treated with placebo



Source: compiled during evaluation; Excel spreadsheet  
*BRCAm* = BRCA1 or BRCA2 mutation; OS = overall survival

- 6.48 The log-logistic model overestimated median survival with olaparib treatment by approximately five months and underestimated median survival with *BRCAm* by approximately 28 months making it a poorly fitting function within the modelling. The submission did not present sensitivity analyses to test other methods of extrapolation, but these were also poorly fitting. The submission used the whole Kaplan-Meier curve to extrapolate the overall survival. There are limitations of using the data from the tail of the Kaplan-Meier curve, where this curve becomes unstable due to decreasing patient numbers. A more appropriate methodology would be to extrapolate overall survival from an earlier time point (where patient numbers are greater), and use a more flexible Royston & Parmar model, which uses multiple points of inflexion (Latimer, 2013). The PSCR (page 5) disagreed with this proposed methodology, and stated that an extrapolation based on 1 degree of freedom (treatment allocation to olaparib or placebo), simply mirrored a Weibull distribution.
- 6.49 The PSCR (pages 5 and 6) reiterated the sponsor’s position that the log-logistic was most appropriate, based on goodness of fit analyses using

Akaike’s Information Criteria (AIC). The PSCR further stated that the log-logistic distribution allows for a changing hazard over time, which better accommodates the initial sharp declines, followed by plateaus observed in PFS and OS survival curves in Study 19. The PSCR further noted that, among olaparib-treated *BRCAM* subjects, the median PFS predicted by log-logistic extrapolation (10.1 months) was reasonably matched to the median PFS observed in Study 19 (8.4 months). Among placebo-treated *BRCAM* subjects, predicted median PFS (4 months) also matched the median PFS observed in Study 19 (4.8 months).

6.50 The ESCs considered that there were substantial issues associated with the extrapolation of overall survival, and that the methods used to generate this pivotal aspect of the economic evaluation were inadequately presented. The ESCs noted the AIC analysis (Table 14), which showed that while the log-normal model was the most appropriate model for progression-free survival, it was a poorer fit than either the log-logistic or Weibull for the extrapolation of overall survival pre- and post-progression. The ESCs considered that each of the presented models produced an unreasonable extrapolation, and that a more appropriate extrapolation would lie somewhere between the log-logistic and the Weibull and log-normal, however noted selecting between the extrapolation options generated a wide range of incremental cost-effectiveness ratio (ICER) results. The Pre-PBAC response argued (page 3) that the ESCs’ assertion that the log-logistic was inappropriate because it was based only on a mismatch between predicted OS and observed OS among placebo-treated *BRCAM* subjects. The response further argued that the ESCs’ approach failed to recognise that OS for placebo-treated subjects in Study 19 was over-estimated because of post-trial treatment switching, and should not serve as a reference against which to validate model outputs.

6.51 The ESCs also considered that the sponsor should clarify precisely which data was used to calculate the AIC (particularly whether sources of data outside Study 19 were incorporated), and should present the corresponding Bayesian Information Criteria (BIC) results. Overall, the ESCs considered the log-logistic extrapolation unjustifiably inflated the modelled incremental benefit and did not align with the observed results of Study 19 represented in the available Kaplan-Meier curves. The Pre-PBAC response clarified (page 4) that only data from Study 19 were used to calculate the AIC. The response also provided the BIC data (see Table 15 below), claiming that it supported the choice of the log-logistic extrapolation. The corresponding AIC data provided in the pre-PBAC response differed from those reported in the submission, but these have not been updated in Table 14. The Pre-PBAC response also asserted that the updated survival curves support the plateau observed in the modelled survival curves.

**Table 14: Akaike Information Criteria (AIC) to evaluate the parametric distributions**

Model	Distribution		
	Log-logistic	Weibull	Log-Normal
Progression-free survival			
Overall survival pre-progression			
Overall survival post-progression			

Source: Table C.8, p176 of the submission

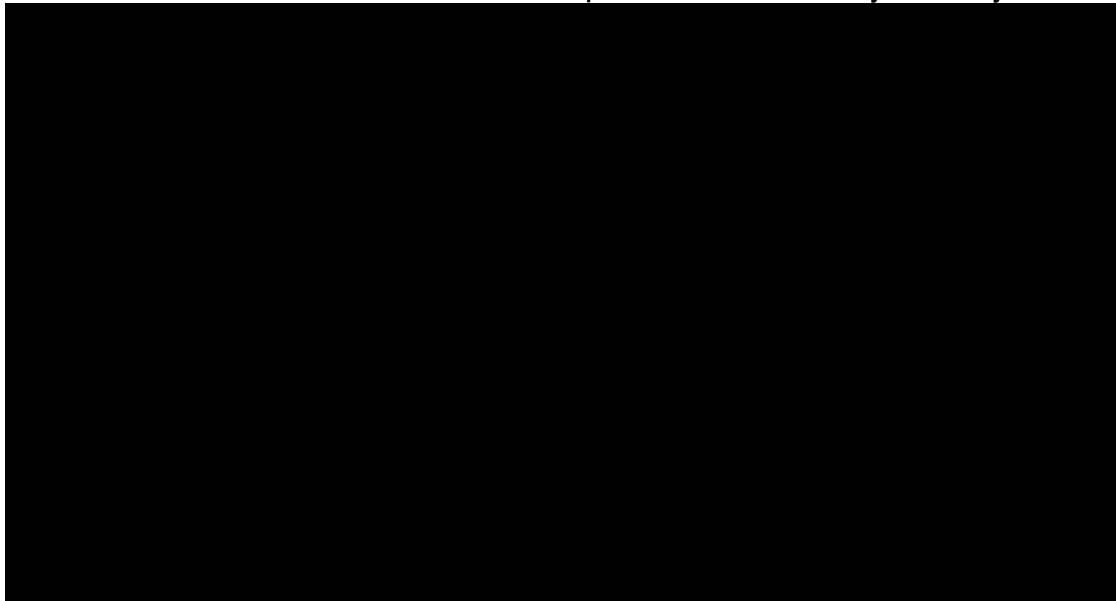
**Table 15: Bayesian Information Criteria (BIC) to evaluate the parametric distributions**

Model	Distribution		
	Log-logistic	Weibull	Log-Normal
Progression-free survival			
Overall survival pre-progression			
Overall survival post-progression			

Source: Pre-PBAC response p4

6.52 The Pre-PBAC response also presented an alternative extrapolation method (page 1 and 3), which derived transition probabilities from Study 19 up until 28.5 months follow-up (ie not updated consistent with Figure 2), after which the log-logistic modelled extrapolations were used (see Figure 5). This resulted in an ICER of \$45,000 - \$75,000 per year of life gained and \$45,000 - \$75,000 per quality-adjusted life year (QALY) gained. In this context, the Pre-PBAC response offered a **█%** rebate on the DPMQ of olaparib to maintain the base case ICER presented in the submission.

**Figure 5: Survival curves for the BRCA/olaparib group and the no BRCA/no olaparib group, based on a model which used initial transition probabilities derived directly from Study 19**



6.53 The ESCs also noted that the utilities used in the economic analysis did not take into account the difference in quality of life between a patient on olaparib maintenance therapy and a patient on placebo. The ESCs noted the Lederman (2014) paper which assessed the health-related quality of life during olaparib maintenance therapy, and considered that each quality of life scale demonstrated a trend (albeit one that was not statistically significant) towards decreased quality of life in the olaparib group pre-progression. The ESCs suggested that the non-significance of the results may have been due to a lack of power. The ESCs considered that, as patients begin olaparib maintenance therapy when they are well (i.e. before their next relapse), a trade-off occurs, where patients accept a lower quality of life for longer survival. The ESCs considered that this trade off should have been captured in the economic model.

6.54 There were two major issues with the methodology to estimate overall survival:

- The submission used only the point estimate of the most optimistic *post hoc* analysis of overall survival (i.e. the 'PARPi sites-excluded method'). Confidence intervals were not applied in the model as it was considered that due to uncertainty this would not be appropriate; and
- The survival extrapolation methodology was inappropriate and made the economic model unreliable.

6.55 The key drivers of the economic model are presented in Table 16.

**Table 16: Key drivers of the model**

Description	Method/Value	Impact
Extrapolation method	Log-logistic curve	High, favours olaparib
Estimation of true OS of olaparib	<i>Post hoc</i> 'PARPi sites excluded method'	High, favours olaparib
Olaparib treatment cost	Mean duration of treatment of Study 19 (18m)	High, favours olaparib

Source: compiled during the evaluation

OS = overall survival; PARPi = polyadenosine 5' diphosphoribose polymerase inhibitor; m = months

6.56 The results of the economic evaluation are presented in Table 17.

**Table 17: Results of the economic evaluation (per person)**

Component	BRCA testing/olaparib	Standard of care	Increment
Costs	\$ [REDACTED]	\$13,798	\$ [REDACTED]
YoLG (discounted)	3.82	2.63	1.19
QALYs gained (discounted)	2.85	1.92	0.93
<b>Incremental cost/per year of life gained (discounted)</b>			<b>\$ [REDACTED]</b>
<b>Incremental cost/per QALY gained (discounted)</b>			<b>\$ [REDACTED]</b>

Source: Table D.15- D.16, pp219-220 of the submission

QALY = quality-adjusted life year; YoLG = year of life gained

The redacted table above shows ICERs in the range of \$45,000/QALY - \$75,000/QALY

6.57 The model estimated a discounted incremental cost-effectiveness ratio (ICER) of \$45,000 - \$75,000 per life year gained and \$45,000 - \$75,000 per quality-adjusted life year (QALY) gained for introducing *BRCA* testing with olaparib (where relevant) versus standard of care. However, the model results did not have internal validity with the interim analysis of patients with *BRCAM* and *BRCAt*/unknown from Study 19. Therefore, the economic model was unreliable.

6.58 The results of the key sensitivity analyses are provided in Table 18.

**Table 18: Results of key univariate sensitivity analyses**

Univariate analyses	Δ costs	Δ QALY	ICER
<b>Base case</b>	\$ [REDACTED]	0.93	\$ [REDACTED]
<b>Model structure</b>			
Time horizon (base case = 10 years)			
5 years	\$ [REDACTED]	0.53	\$ [REDACTED]
7 years	\$ [REDACTED]	0.70	\$ [REDACTED]
15 years	\$ [REDACTED]	1.22	\$ [REDACTED]
HR for OS for <i>BRCAM</i> (base case = 'PARPi sites-excluded method', Upper 95% CI of 'PARPi sites-excluded method' (0.96) Lower 95% CI of 'PARPi sites-excluded method' (0.28) Derived from RPSFT method (0.664) <i>BRCAM</i> subgroup: unadjusted results (HR; 0.73) Upper 95% CI of unadjusted hazard ratio (1.17) Lower 95% CI of unadjusted hazard ratio (0.45)	HR: 0.52 \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED]	0.25 1.43 0.66 0.56 0.04 1.07	\$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED]
Extrapolation method (base case = log-logistic)			
Weibull	\$ [REDACTED]	0.30	\$ [REDACTED]
Lognormal	\$ [REDACTED]	0.54	\$ [REDACTED]
<b>Model inputs</b>			
Cost of olaparib until disease progression (base case = 18 cycles)	\$ [REDACTED]	0.93	\$ [REDACTED]

Source: Table D.17, p222-223 of the submission

*BRCAM* = *BRCA1* or *BRCA2* mutation; CI = confidence interval; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OS = overall survival; PARPi = polyadenosine 5' diphosphoribose polymerase inhibitor; QALY = quality-adjusted life year; RPSFT = rank preserving structural failure time; Δ = incremental

- 6.59 The results of the sensitivity analyses indicated that the model was most sensitive to the extrapolation of overall survival, the method used to adjust for patient crossover, the duration of olaparib treatment and the time horizon. The base case model used the most favourable method for all these key issues.

**Drug cost/patient/course: \$ [REDACTED]**

- 6.60 The drug cost per patient per course was based on the mean duration of treatment among *BRCAM* patients in Study 19 of [REDACTED] months, an effective dispensed price of maximum quantity (DPMQ) of \$ [REDACTED] and a dose intensity of 84.5%. The treatment time for olaparib in clinical practice could be longer as treatment can continue until disease progression and ~[REDACTED]% of the patients in the *BRCAM* group of Study 19 were still on treatment at the end of the trial (~4 years).

**Estimated extent of use and financial implications**

- 6.61 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the expected financial impact of *BRCA* testing and olaparib, over a five year period (Table 19).

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use <i>BRCA</i> test</b>					
Eligible population <sup>a</sup>					
Number of <i>BRCA</i> tests (90% uptake)					
<b>Estimated extent of use, olaparib</b>					
Eligible population <sup>b</sup>					
Uptake of olaparib	75%	80%	85%	90%	90%
Number treated					
Scripts (1 pack per script)					
<b>Estimated net cost to PBS/RPBS/ MBS</b>					
Net cost to MBS (\$ per test)	\$	\$	\$	\$	\$
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
<b>Estimated total net cost</b>					
<b>Total net cost to Government</b>	\$	\$	\$	\$	\$

Source: Table E.11- E.13 pp223-224; Table E.18. p293 of the submission

*BRCA*m = *BRCA*1 or *BRCA*2 mutation; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PSR = platinum-sensitive relapsed; RPBS = Repatriation Pharmaceutical Benefits Scheme

<sup>a</sup> PSR ovarian cancer

<sup>b</sup> *BRCA*m PSR ovarian cancer

The redacted table above shows that by year 5, the estimated number of patients would be less than 10,000 and the net cost to PBS would be \$10-\$20 million.

6.62 The submission estimated that if *BRCA* testing and olaparib were both listed, the net cost to the MBS would be approximately less than \$10 million dollars over the first five years.

6.63 The submission estimated the net cost of listing olaparib in the PBS/RPBS would be approximately \$60 - \$100 million over the first five years.

6.64 The submission estimated the overall net cost of *BRCA* testing and olaparib to the Government would be approximately more than \$100 million dollars over the first five years. The annual cost was expected to peak at \$20-\$30 million in Year 2, due to the prevalent population from Year 1 and Year 2. Reasons why the financial estimates were considered uncertain were that:

- the cost of treating disease progression with subsequent chemotherapy was not included in the financial estimates (estimated at 45% of total costs by Doyle, 2001). The PSCR (page 8) argued that patients would receive further lines of therapy upon progression regardless of the availability of olaparib, and thus it does not represent a new cost. The ESCs agreed that it was appropriate to not include the cost of subsequent lines of chemotherapy;
- the sample size of the (n = ) used to estimate the patient inflows. The PSCR (page 8) argued this small sample size was due to the rarity of the disease;
- the cost of treating adverse events were not included in the financial estimates; previous evidence found these costs to be a key contributor of total costs (Weycker, 2008);
- if a biopsy is necessary to obtain a tumour sample then this might increase the cost to the MBS; and

- the accuracy of the estimation of the incident ovarian cancer population from AIHW data, which excluded fallopian tube and primary peritoneal cancers. The PSCR (page 8) acknowledged the estimation of the incident population inadvertently excluded patients with fallopian tube and primary peritoneal cancers due to a change in AIHW classification, and revised the financial estimates by multiplying the previous estimated patient number by 16% (reflecting the Study 19 population), to account for the excluded patients. The revised financial estimates are presented below.

**Table 20: Updated estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients treated with olaparib					
NET cost to PBS	\$	\$	\$	\$	\$
NET cost to MBS	\$	\$	\$	\$	\$
NET cost to Government	\$	\$	\$	\$	\$

Source: Pre-Sub-Committee Response p.11

The redacted table above shows that at year 5, the estimated number of patients would be less than 10,000 and the net cost to PBS would be \$10-\$20 million.

- 6.65 The revised financial estimates, including patients with fallopian tube and primary peritoneal cancer, estimated the net cost of listing olaparib on the PBS/RPBS would be approximately more than \$100 million over the first five years. The overall net cost of *BRCA* testing and olaparib to the Government would be approximately more than \$100 million over the first five years.

**Quality Use of Medicines**

- 6.66 The submission stated that *BRCA* testing, to inform maintenance treatment with olaparib in patients with *BRCAm* platinum-sensitive relapsed ovarian cancer, is expected to change the clinical paradigm. This could lead to increased pressure on the hospital system and potential delays in obtaining *BRCA* testing results. The submission stated the sponsor has collaborated with key stakeholders to facilitate the timely access to *BRCA* testing.
- 6.67 An additional quality use of medicine issue, not further discussed in the submission, is that patients would be required to take eight capsules twice a day, totalling 16 capsules per day. In Study 19, common gastrointestinal side effects with olaparib treatment (ITT) were nausea (70.6%), vomiting (33.8%), and diarrhoea (27.2%). These gastrointestinal side effects could have a significant impact on the compliance to olaparib treatment. Further, within the clinical trial, patients who were unable to swallow oral medication and patients with gastrointestinal malabsorption were excluded. The ESCs agreed that this ‘pill burden’ would present an important quality use of medicines issue, particularly in the context of the gastrointestinal side effects associated with olaparib treatment.

### **Financial Management – Risk Sharing Arrangements**

- 6.68 The submission stated that the sponsor was willing to work with the Department to determine a risk sharing arrangement related to potential uncertainty of the estimated eligible population for olaparib. The sponsor proposed a percentage rebate on any expenditure above an agreed threshold on eligible patient numbers for the requested indication.
- 6.69 The Pre-PBAC (page 1 and 5) response suggested that uncertainty around mean treatment duration and the corresponding drug costs could be managed through a risk sharing arrangement.
- 6.70 The PBAC considered that a cap would need to be applied to manage the uncertainty around the predicted treatment duration, whereby after patients have received two years of subsidised treatment with olaparib, a 100% rebate would be required for any further time spent on treatment.

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

## **7 PBAC Outcome**

- 7.1 The PBAC deferred its decision on whether olaparib should be listed in the Pharmaceutical Benefits Schedule for the treatment of high grade serous ovarian, fallopian tube or primary peritoneal cancer. The PBAC considered that there was a strong clinical need for an oral maintenance treatment with manageable adverse events like olaparib, and the updated data demonstrated an improvement in overall survival in the requested *BRCAm* subgroup. However, the incremental cost-effectiveness ratio was substantially underestimated and unacceptably high at the price proposed because of concerns with key aspects of the modelled economic evaluation which would need to be addressed before the PBAC could complete its decision.
- 7.2 The PBAC accepted that standard follow up care (placebo) was the appropriate comparator.
- 7.3 The PBAC noted that, on the basis of the ITT population from the head-to-head trial comparing olaparib with placebo (Study 19), the median progression-free survival and overall survival for women on olaparib were approximately 8.4 months and 29.8 months, respectively; whereas median progression-free survival and overall survival for women on placebo were 4.8 months and 27.8 months, respectively. The PBAC further noted that, for every 100 patients treated with olaparib in comparison with placebo over a 37.3 months median duration of follow-up, there were:
- approximately four additional Grade 3 or higher cases of fatigue;
  - approximately four additional Grade 3 or higher cases of anaemia; and
  - approximately three additional Grade 3 or higher cases of neutropenia.
- 7.4 The PBAC noted the ESCs' concerns around the long-term safety of olaparib in the context of MDS and AML, however also accepted the Pre-PBAC response's argument (page 2) that MDS and AML are also recognised side

effects of conventional chemotherapy, and noted that the reported incidence for ovarian cancer patients definitely known to have received olaparib was 0.78%, compared with 1.3% of ovarian cancer patients who did not receive olaparib. The PBAC considered these concerns to be theoretically sound at this point in time and so should be the subject of standard post-marketing surveillance, but were not sufficient to impede support for subsidising olaparib as requested.

- 7.5 The PBAC noted that patients would be required to take eight capsules twice a day, totalling 16 capsules per day and that the ESCs considered this ‘pill burden’ would present an important quality use of medicines issue, particularly in the context of the gastrointestinal side effects associated with olaparib treatment. The PBAC, however, considered that in the context of the disease being treated, this was a manageable issue.
- 7.6 The PBAC noted that there was missing *BRCA* data for the *BRCA*wt/unknown subgroup. The PBAC noted the sponsor’s argument that data was only missing for 11 out of 265 participants (4%), and considered that this provided sufficient basis to assess the effectiveness of olaparib across the *BRCA* subgroups. However, the PBAC also agreed with the ESCs that 108 participants (41%) had either missing or unknown test results when broken down by type of testing (tumour or germline) and considered that this reduced confidence in the assessment of test performance, particularly given that many of the *BRCA* results were obtained after the completion of Study 19. Furthermore, the PBAC noted that the *BRCA* mutation status was not determined in a consistent manner for all cases. Specifically, *BRCA* mutant status was compiled retrospectively using either/and a) local case reports of germline status (method not reported), b) germline testing (Myriad genetics Integrated *BRCA* analysis assay), c) tumour testing (FPEPE Foundation medicine and Illumina HiSeq). Overall 70% (96/136) patients were considered *BRCA*m on the basis of a germline test result and a further 22 individuals (22/136, 16%) who did not have germline DNA available were reported as *BRCA*m on the basis of a tumour test result. The final 18 additional *BRCA*m cases were identified from a positive tumour test and a negative germline screen. No data was presented to explain whether the “false negative” germline test results in these 18 individuals occurred because of germline testing issues or were truly reflective of somatic mutations. The PBAC considered that, in clinical practice, germline DNA would always be available for testing. The PBAC also noted that, in contrast to germline *BRCA* testing, *BRCA* testing of tumour tissue is not standardised in pathology practice. PBAC referred further commentary on this matter to the Medical Services Advisory Committee (MSAC).
- 7.7 The PBAC was also concerned about *BRCA* mutation variants of unknown significance which were assigned “wild-type” status for the purposes of Study 19. If these mutations are interpreted as pathogenic in Australian practice, inappropriate treatment decisions will be made. In this context, the PBAC considered that any PBS-subsidised access to olaparib would need to be restricted to patients classified as having “likely pathogenic” or “definitely pathogenic” (class 4 or 5 according to the five-class system proposed by Plon et al, Hum Mutat. 2008 Nov;29(11):1282-91) *BRCA* mutations. This will ensure that treatment is targeted to those who will likely benefit.

- 7.8 With regards to the claim of co-dependence, the PBAC noted that the PFS benefit observed in the Study 19 *BRCAM* subgroup (HR: 0.18) was greater than that observed in the ITT population (HR: 0.35) and in the complementary *BRCAwT/unknown* subgroup (HR: 0.54), with the interaction test performed for *BRCA* status group by PFS effect being statistically significant ( $p=0.03$ ). The PBAC considered that it was biologically plausible that olaparib would be more efficacious in *BRCAM* patients, and noted that it had been registered for use in this subgroup by the FDA and the TGA. In this context, the PBAC accepted that any PBS-subsidy of olaparib treatment would need to be confined to *BRCAM* patients.
- 7.9 The PBAC noted that the Pre-PBAC response agreed with the ESCs' suggestion to restrict MBS listing to germline *BRCA* testing only. The PBAC considered that germline DNA testing is readily available in clinical practice and germline testing is a less expensive, standardised, reproducible and interpretable test compared with tumour testing. The PBAC noted that *BRCAM* status is being used as a surrogate for defective homologous DNA repair in the tumour. The finding of a single mutation in the *BRCA* gene (using germline or tumour DNA) does not necessarily signify defective homologous DNA repair in the tumour. Despite these limitations, the PBAC accepted the biological plausibility of using *BRCAM* status as a surrogate for homologous DNA repair deficiency, and considered that germline testing was the most appropriate means to identify such patients.
- 7.10 The PBAC therefore advised that the following foreshadowed recommendation would be relevant to MSAC deliberations: to limit, amongst other criteria, any PBS-subsidised access to olaparib to patients who have a germline *BRCA* mutation (class 4 or 5 mutations only).
- 7.11 The PBAC agreed with the ESCs that the use of RECIST to determine progression may be impractical in clinical practice. However, as a consequence, the PBAC advised that the subjective assessment of whether a patient has stable or responding disease would mean that the mean duration of olaparib treatment would likely extend beyond that predicted by Study 19, but with likely diminishing marginal effectiveness.
- 7.12 The PBAC noted that the economic model estimated an incremental cost-effectiveness ratio (ICER) of \$45,000 - \$75,000 per life year gained and \$45,000 - \$75,000 per QALY gained for introducing *BRCA* testing and olaparib (when relevant) versus current standard of care. The PBAC noted that the model was shown to be most sensitive to the extrapolation of overall survival, the method used to adjust for patients randomised to placebo crossing over to receive a PARP inhibitor, the duration of olaparib treatment, and the time horizon.
- 7.13 The PBAC agreed with the ESCs' advice that the log-logistic extrapolation used in the model unjustifiably inflated the modelled incremental benefit and did not align with the observed results of Study 19. The PBAC also noted that the alternative extrapolation provided in Pre-PBAC response (page 1 and 3) using initial transition probabilities derived from the early results of Study 19, resulted in an ICER of \$45,000 - \$75,000 per life year gained and \$45,000 -

\$75,000 per QALY gained. In this context, the Pre-PBAC response offered a █% rebate on the DPMQ of olaparib to maintain the base case ICER presented in the submission. However, in comparing Figure 2 (████████████████████) and Figure 5 (modelled overall survival estimates up to 10 years), the model can be seen to clearly overestimate the observed incremental overall survival for olaparib over its comparator. This conclusion was unchanged when the modelled estimates were compared with the observed survival results in the ‘sites excluded’ analysis to adjust for patient crossover. The PBAC considered that the arguments provided in the PSCR and the pre-PBAC Response, to support the modelled extrapolation, were insufficient to address this primary concern.

- 7.14 The PBAC noted the ESCs’ concerns around the ‘sites excluded’ analysis to adjust for patient crossover, however considered that, on balance, the data from Study 19 demonstrated that olaparib results in a significant improvement in PFS and a likely improvement in OS in the *BRCAm* subgroup. The PBAC also considered that the updated OS data presented in the PSCR and the Kaplan-Meier curves presented in the Pre-PBAC response (attachment 1) further supported this conclusion. The PBAC considered in the context of this submission that, although neither the ‘sites excluded’ nor the corresponding ‘sites included’ analysis could provide conclusive results, patient crossover was not the greatest source of uncertainty regarding the estimate of incremental overall survival for olaparib over its comparator.
- 7.15 The PBAC noted that the updated OS data showed an ██████████ in truncated mean treatment duration from ████ to approximately ████ days and agreed with the ESCs’ advice that it would be reasonable to expect that patients would remain on treatment longer than the truncated mean treatment duration observed in Study 19 to date. The PBAC also noted the pre-PBAC response’s suggestion (page 1 and 5) that uncertainty around mean treatment duration and the corresponding drug costs could be managed through a risk sharing arrangement.
- 7.16 The PBAC noted the ESCs’ advice that a time horizon of 10 years may not be conservative and is likely to bias in favour of olaparib. The sponsor argued that Australian and international data provide strong evidence that a substantial number of patients with advanced ovarian cancer remain alive at 10 years, however, the PBAC agreed with ESC that the 10-year time horizon was not conservative because the shape of the extrapolations prolonged the overestimated incremental overall survival beyond the observed results provided in the updated results.
- 7.17 The PBAC also accepted the ESC advice that the model favoured olaparib to an extent not examined in any sensitivity analysis, because it assigned the same utility value to being on olaparib maintenance therapy as to being on placebo (ie not being on maintenance treatment) despite the identified symptomatic adverse effect profile identified for olaparib.
- 7.18 The PBAC concluded that the modelled economic evaluation as provided in the submission, and as varied in the PSCR, substantially underestimated the true ICER mostly because it overestimated incremental survival and then prolonged this overestimate over a long time horizon, and it underestimated

the duration and thus cost of olaparib in the context of likely diminishing marginal effectiveness. In this context, the PBAC considered that the mitigating offers of a █% rebate and a possible risk sharing arrangement to cap olaparib costs beyond a defined treatment duration were insufficient to enable it to recommend that olaparib be listed.

- 7.19 Noting the strong clinical need and the updated evidence of incremental effectiveness, the multiple factors contributing to an underestimated ICER, and the mitigating offers from the sponsor, the PBAC decided to defer the submission in order to obtain further input from the sponsor mostly on how the ICER might be kept in the range of the base case provided whilst also particularly correcting for the overestimated incremental overall survival, and also to (a) suggest an administratively simple means of applying a 100% rebate beyond an olaparib treatment duration cap of two years, and (b) revise the financial estimates to reflect the restricted patient population (i.e. patients with germline class 4 or 5 *BRCA* mutations only).
- 7.20 In order to provide some guidance to the sponsor about how its main concern might be addressed, the PBAC suggested two scenarios. A minor submission might be appropriate if the submitted model was used with a truncated time horizon of 7.5 years were to be lodged, with a price reduction to keep the resulting ICER at \$45,000 - \$75,000 per QALY gained. Conversely, a major submission would be needed to use the latest OS data from Study 19 up to about 66 months of follow-up before then justifying an appropriate extrapolation method to then also estimate a price reduction to keep the resulting ICER at \$45,000 - \$75,000 per QALY gained.
- 7.21 The PBAC noted that the *BRCA* test component of the integrated co-dependent submission would be considered by MSAC at its March 2016 meeting.

**Outcome:**

Deferred

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

The sponsor had no comment.