

6.10 PERTUZUMAB, Solution for IV infusion, 420mg in 14 mL, Perjeta[®], Roche Products Pty Ltd.

1 Purpose of Application

- 1.1 Section 100 (Efficient Funding of Chemotherapy), Authority Required, listing for pertuzumab for the treatment of human epidermal growth factor 2 (HER2) positive, lymph node positive, early breast cancer (eBC). Pertuzumab has not been previously considered for this indication.
- 1.2 The basis for listing was cost-effectiveness of pertuzumab in combination with trastuzumab and chemotherapy (Ptz+T+Chemo) compared to trastuzumab in combination with chemotherapy (T+Chemo).

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

Component	Description
Population	Patients with HER2 positive, lymph node positive, eBC
Intervention	Pertuzumab in combination with trastuzumab and chemotherapy (Ptz+T+Chemo) for the adjuvant treatment of eBC for up to 52 weeks
Comparator	Trastuzumab in combination with chemotherapy (T+Chemo)
Outcomes	Primary endpoint: iDFS Secondary endpoints: OS, RFI, DRFI, AEs Health-related QoL
Clinical claim	Pertuzumab significantly improved the rates of iDFS among patients with HER2 positive, lymph node positive, (operable) early breast cancer when it was added to trastuzumab and chemotherapy in the adjuvant setting

AE= Adverse event; DFRI= Distant relapse-free interval; DFS= Disease-free survival; eBC= early breast cancer; HER2= human epidermal growth factor; iDFS= Invasive disease-free survival; OS= Overall survival; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; QoL= Quality of Life; RFI= Relapse-free interval; T+Chemo= trastuzumab and chemotherapy. Source: Table 1.1.1, p15 of the submission.

2 Requested listing

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

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	DPMA	Proprietary name	Manufacturer
Pertuzumab HER2 positive early breast cancer Solution for intravenous infusion 420 mg in 14 mL	840 mg	0	Public: \$6,229 Private: \$6,353	PERJETA®	Roche Products Pty Ltd
Category/Program	Section 100 (Public/Private)– Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required Public Hospital Authority Required				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
Severity	Early				
Condition:	HER2 positive early breast cancer				

Indication	Early HER2 positive breast cancer
Treatment phase:	Initial treatment (3 weekly regimen)
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" 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 type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) in the primary tumour, AND Patient must have evidence of lymph node status as demonstrated by a report documenting ≥ 1 positive node, AND Patient must commence treatment concurrently with adjuvant chemotherapy plus trastuzumab, AND <i>Patient must commence treatment concurrently with trastuzumab</i> AND Patient must have undergone surgery, AND The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure, AND Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy.</p>
Administrative Advice	<p>Authority applications for initial treatment must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and (b) a completed Early Breast Cancer - PBS Supporting Information Form which includes:</p> <p>(i) a copy of the pathology report from an Approved Pathology Authority confirming the presence of HER2 gene amplification by in situ hybridisation (ISH); and (ii) a copy of the signed patient acknowledgement form.</p> <p>Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval and then at 3 monthly intervals during treatment.</p>

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	DPMA	Proprietary name	Manufacturer
Pertuzumab HER2 positive early breast cancer Solution for intravenous infusion 420 mg in 14 mL	420 mg	3	Public: \$3,156 Private: \$3,238	PERJETA®	Roche Products Pty Ltd
Category/Program	Section 100 (Public/Private)– Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required Public Hospital Authority Required				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
Episodicity:	Adjuvant treatment				
Severity	Early				
Condition:	HER2 positive early breast cancer				

Indication	Early HER2 positive breast cancer
Treatment phase:	Continuing treatment (3 weekly regimen)
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" 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 type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug AND The treatment must be in combination with chemotherapy and trastuzumab AND The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure AND Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy.</p>
Administrative Advice:	<p>A patient who has a treatment break of less than 6 weeks in PBS-subsidised treatment with this drug for reasons other than disease progression is eligible to continue to receive PBS-subsidised treatment with this drug.</p> <p>A patient who has a treatment break of more than 6 weeks in PBS-subsidised treatment with this drug is not eligible to receive PBS-subsidised treatment with this drug.</p> <p>Where a patient has had a treatment break the length of the break is measured from the date the most recent treatment was stopped to the date of the application for further treatment.</p> <p>Cardiac function must be tested by a suitable method including, for example, ECHO or MUGA, at 3 monthly intervals during treatment.</p>

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	DPMA	Proprietary name	Manufacturer
Pertuzumab HER2 positive early breast cancer Solution for intravenous infusion 420 mg in 14 mL	420 mg	3	Public: \$3,156 Private: \$3,238	PERJETA®	Roche Products Pty Ltd
Category/Program	Section 100 (Public/Private)– Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required Public Hospital Authority Required				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
Episodicity:	Adjuvant treatment				
Severity	Early				
Condition:	HER2 positive early breast cancer				
Indication	Early HER2 positive breast cancer				
Treatment phase:	Grandfathering treatment				

Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" 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 type="checkbox"/> Streamlined
Clinical criteria:	<p><i>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition before [listing date]</i></p> <p>AND</p> <p>Patient must have evidence of lymph node status as demonstrated by a report documenting ≥ 1 positive node,</p> <p>Patient must have previously received treatment with non-PBS-listed pertuzumab</p> <p>AND</p> <p>The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure</p> <p>AND</p> <p>The treatment must be in combination with chemotherapy and trastuzumab</p> <p>AND</p> <p>Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy.</p>
Administrative Advice	<p>Authority applications for treatment must be made in writing and must include a completed authority prescription form and a copy of the signed patient acknowledgement form.</p> <p>Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), at 3 monthly intervals during treatment.</p>

2.1 The proposed initial PBS restriction requires patients to have ≥ 1 positive lymph nodes. This is narrower than the TGA indication proposed at submission lodgement and the PBS restriction for trastuzumab for eBC in terms of lymph node status. The sponsor stated that the definition of “high risk” in the revised TGA indication encompasses the patient population with positive lymph node status (Pre-Sub-Committee Response, PSCR). It is not known how many high risk patients defined by the TGA indication are not covered by the PBS restriction, which may be relevant in the context of utilisation and financial estimates. The DUSC considered that there may be use outside of the proposed restriction in patients without lymph node involvement. The METIS survey provided in the submission revealed that ■% to ■% of surveyed oncologists would treat patients with node negative HER2+ eBC with pertuzumab even if it were PBS listed only for node positive patients. The PBAC accepted that the definition of “high risk patients” would include patients with lymph node positive status. Therefore, the PBAC considered it was reasonable to restrict pertuzumab to patients with HER2 positive eBC who have positive lymph node status. The PBAC also noted the DUSC’s advice that HER2 gene status and lymph node status are not always on the same report, so the restriction should include the requirement to provide a copy of the lymph node status report. Therefore, the PBAC considered the criterion “Patient must have evidence of lymph node status as demonstrated by a report documenting ≥ 1 positive node” was appropriate to include in the restriction. In addition, the Early Breast Cancer - PBS Supporting Information Form and Administrative Advice would require updating for inclusion of evidence of lymph node status, based on the currently proposed restriction.

2.2 The proposed initial PBS restriction intends to be aligned as much as possible with the current pertuzumab and trastuzumab listings, however it is not consistent with the eligibility criteria in the APHINITY trial presented in the submission in terms of the following:

- The APHINITY trial excluded patients with a baseline left ventricular ejection fraction (LVEF) < 55% (the proposed PBS restriction excludes patients with a baseline LVEF < 45%). The ESC noted that the proposed criterion is aligned with the current trastuzumab listing. The ESC also noted the study by Chien, 2016¹, where the trastuzumab-related heart failure (HF) and/or cardiomyopathy (CM) rate was 5-fold lower in a Taiwanese cohort compared to a US-based study, while the cohorts has a similar risk of trastuzumab-related HF and/or CM. The submission acknowledged there was a difference in ethnicity between the trial and the Australian HER2 positive early breast cancer population but suggested that this difference was unlikely to have an effect. The PBAC considered there may be higher rates of HF and CM in the Australian population than seen in the trial. The PBAC considered it may be more appropriate to align the LVEF criterion for pertuzumab with the APHINITY criterion.
- The APHINITY trial did not require patients to have ≥1 positive lymph nodes (the proposed PBS restriction requires patients to have ≥1 positive lymph nodes). As noted above, the PSCR stated that the proposed TGA indication has been revised to narrow the eligible population to “high risk” patients.
- The APHINITY trial confirmed HER2 status using immunohistochemistry (IHC) 3+ or in situ hybridisation (ISH) (the proposed PBS restriction and related MBS item 73332 requires HER2 status to be confirmed using only ISH).
- The APHINITY trial excluded patients with Eastern Cooperative Oncology Group (ECOG) performance status > 1 (the proposed PBS restriction did not include ECOG performance status). The ESC considered that, with the proposed restriction, the vast majority of patients with early breast cancer would have a performance status ≤1. The PBAC considered that it was reasonable to not include an ECOG performance status to align with the current trastuzumab restriction.

2.3 The proposed continuing PBS restriction requires patients to be concurrently receiving chemotherapy. Most concurrent chemotherapies would be ceased after around 4-6 months of therapy. The PBS restriction for trastuzumab for eBC does not have this restriction. This criterion of concurrent chemotherapies could be removed so that patients can continue to meet the criteria of the continuing PBS restriction; the PSCR affirms support for this change and this has been removed from the continuing and grandfather restrictions above.

¹ Chien HC, Kao Yang YH, Bai JP. Trastuzumab-Related Cardiotoxic Effects in Taiwanese Women: A Nationwide Cohort Study. *JAMA Oncol.* 2016 Oct 1;2(10):1317-1325

- 2.4 The ESC noted that a 6 week break has been allowed for patients using pertuzumab in the proposed continuing restriction. This is consistent with the restriction for trastuzumab for early breast cancer which includes “Where a patient has a break in trastuzumab therapy of more than 1 week but less than 6 weeks from when the last dose was due, authority approval will be granted for a new loading dose”. The PBAC considered it appropriate for a 6 week break to be allowed for pertuzumab and that subsequent therapy can be subsidised if the break does not exceed 6 weeks.
- 2.5 DUSC considered that the restriction did not clarify whether eBC patients at high risk of recurrence who had already started trastuzumab + chemotherapy (but not yet completed 52 weeks of trastuzumab) would be eligible to switch to pertuzumab + trastuzumab + chemotherapy for the remaining duration of their current treatment course. DUSC noted that the APHINITY trial specifically excluded patients with prior use of anti-HER2 therapy or previous systemic chemotherapy. The submission estimates did not consider this group of patients. The pre-PBAC response stated that clinicians have advised that there is no additional prognostic information that would warrant the addition of pertuzumab following initiation of trastuzumab. The decision to treat with pertuzumab would be made upfront considering all the risk factors at the time of diagnosis. The sponsor was open to addressing use outside of the proposed restriction through a risk sharing agreement. The PBAC noted the concern of the DUSC and agreed, unless evidence of efficacy becomes available, that the restriction (initial and grandfather) should clarify that only patients starting pertuzumab and trastuzumab at the same time would be eligible for subsidy, in addition to the criterion ‘Patient must commence treatment concurrently with trastuzumab’.
- 2.6 At its March 2017 meeting, the PBAC considered the DUSC analysis of medicines for the treatment of HER2 positive metastatic breast cancer (item 10.06). The PBAC recommended that the current restriction for initial approval of trastuzumab in early breast cancer be changed from a written authority to a telephone authority. The PBAC noted that this would expedite commencement of neoadjuvant/adjuvant trastuzumab-based therapy. However, the PBAC considered it was not appropriate to change the restriction level for late stage breast cancer, given co-prescription of trastuzumab with pertuzumab in this setting. The PBAC supported removing the grandfather restrictions for trastuzumab, trastuzumab emtansine and pertuzumab. In regards to this submission, the PBAC considered that pertuzumab for early breast cancer should be a written authority. The PBAC noted that because of the difference in prescribing authority, clinicians will have to prescribe pertuzumab as a written authority and trastuzumab as a telephone authority.
- 2.7 The submission proposed a price discount for [REDACTED]. While it is likely that the price of trastuzumab will reduce in the near future following registration of biosimilar medicines, which would impact on the overall cost, this was not considered in the analysis presented in the submission and stated by the sponsor to be additional cost savings if and when that occurred.

- 2.8 In addition, trastuzumab met the criteria for a 10% statutory price reduction on 1 June 2018 under sections 99ACF and 99ACL(1) of Division 3A of Part VII of the National Health Act 1953 (Ten Year Anniversary Price Reductions). At the time of submission, this reduction had not occurred, therefore the model results as well as financial estimates were calculated using the price of trastuzumab prior to 1 June 2018. The pre-PBAC response presented revised financial estimates which takes into account the 10% statutory price reduction on trastuzumab which occurred on 1 June 2018.
- 2.9 The effect of the 1 June 2018 price change for trastuzumab (published AEMP \$352.33 for 60 mg vial and \$880.83 for 150 mg vial) has implications for the (existing) proposed pricing for pertuzumab achieving its stated aim of cost effectiveness with budget neutrality (see Financial Management section).
- 2.10 Table 2 presents the price discounts applied in different sections of the submission. It is not clear how the [REDACTED]% discount is related to the [REDACTED]% discount (updated to [REDACTED]% in the pre-PBAC response), but appears to have been presented to indicate what the submission claimed to be a cost-effective ICER/QALY.

Table 2: Price discount rates on trastuzumab applied in the submission with prices before 1 June 2018

Discount	Patients receiving PBS items: 4650R, 4703M, 7266K, 7267L, 10682F, 10721G, 10743K, 10744L	Section 3 Economic evaluation	Section 4 Financial estimates	Section 5 Financial Management
0%	-	Step 1 – Step 7 of the economic model. Step 7 ICER = \$75,000/QALY – \$105,000/QALY gained	Applied in main analysis (published prices) Net cost = more than \$100 million	-
█%*	Lymph node positive patients (Treated with Ptz+T+Chemo)	Step 8 of the economic model. ICER = \$45,000/QALY – \$75,000/QALY gained	Applied as sensitivity analysis. Net cost = more than \$100	-
█%**	Lymph node positive patients (Treated with Ptz+T+Chemo)	Step 9 of the economic model. ICER = dominant	Applied in main analysis (effective prices). Net cost = \$20 – \$30 million	-
█%***	All patients Lymph node positive patients (Treated with Ptz+T+Chemo) Lymph node negative patients (Treated with T+Chemo)	Not applied	Not applied	Proportion lymph node positive patients (█%) x █% + (1-█%) x 0% = █%

*The █% pricing discount was applied to Trastuzumab in the Ptz+T+Chemo arm to achieve a cost-effectiveness ICER
 **The █% pricing discount was applied to Trastuzumab in the Ptz+T+Chemo arm, for HER2 positive, lymph node positive, eBC patients. A pricing █ was applied to achieve a dominant ICER and budget neutrality.

***In order to practically implement the proposed price discount (█%) to achieve budget neutrality, a price discount of █% was proposed to be applied across all eBC trastuzumab PBS expenditure (PBS Items for '3 weekly regimen' listings: 4650R, 4703M, 7266K, 7267L, 10682F, 10721G, 10743K, 10744L, respectively) (including both lymph node positive (treated with Ptz+T+Chemo) and lymph node negative (treated with T+Chemo))

Source: Table 3.8.6 and 3.8.7, p111 and Table 5.2.2, p151 of the submission, Utilisation and cost model.xlsx and compiled during the evaluation.

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

3 Background

Registration status

- 3.1 The submission was made under TGA/PBAC Parallel Process.
- 3.2 At the time of evaluation for PBAC consideration, the TGA Clinical Evaluation Report (Round 1) was available. The report recommended that “the current application to expand the use of pertuzumab for the adjuvant treatment of early breast cancer █

█

. The PSQR indicated that in

discussions with the TGA, and consistent with other jurisdictions (Committee for Medicinal Products for Human Use (CHMP), Food and Drug Administration (FDA)), the TGA is considering the sponsor's proposal to restrict adjuvant use of pertuzumab to the subgroup of "high risk" patients. The proposed TGA indication for pertuzumab in combination with trastuzumab and chemotherapy is for "the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence". This appears to be on the basis of the results for node positive or hormone receptor negative (HR-) patients in whom the clinical benefit of adjuvant pertuzumab appeared greater, with the TGA Clinical Evaluator indicating that "this subgroup of patients would be those willing to experience the additional toxicity for some important risk reduction from a higher baseline risk level" (TGA Clinical Evaluation Report). The ESC considered the extent of clinical and practical difference between a "high risk" patient population and those prospectively defined in the APHINITY trial and proposed for PBS listing (lymph node positive) is unclear. The sponsor indicated that the lymph node positive population is encompassed within the "high risk" population. The PBAC considered that the "high risk" population included the lymph node positive population and the proposed restrictions have included a criterion to allow this population access to treatment. However, if a definition of "high risk" population is presented in the final product information, further changes to the restriction may be required to include these definitions.

- 3.3 The TGA Delegates Overview for the adjuvant treatment of HER2 positive eBC indication was available at the time of PBAC consideration. The TGA Delegate considered that there was "no reason to say, at this time, that the application to extend the indications for Perjeta should not be approved for registration." Final registration details are expected in September 2018.

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

4 Population and disease

- 4.1 In 2017 it is estimated that approximately 17,586 women and 144 men will be diagnosed with breast cancer (AIHW 2017d). In Australia approximately 94% of breast cancer patients are diagnosed with eBC (Walters 2013).
- 4.2 Early metastatic relapse in HER2 positive eBC is associated with young age at diagnosis, lymph node positive disease and Central Nervous System (CNS) metastases (Lok 2017). Lymph node involvement is considered to be the most important prognostic factor for risk of relapse in breast cancer (CCS 2017; NCCN 2017b). The submission estimated that █% of patients diagnosed with breast cancer in Australia are lymph node positive (Roche breast cancer Advisory board meeting held in 2017; and the Q3 2017 data update from the IPSOS global oncology monitor in Australia). The proportion of patients with lymph node positive disease is uncertain. The AIHW & NBCC (2007) estimated the proportion to be 39% and Chan (2012) estimated the proportion to be 54%.
- 4.3 HER2 is a transmembrane receptor tyrosine kinase, involved in mediating growth, differentiation and survival of cells. In Australia approximately 15% of

breast cancer patients are HER2 positive (Bilous 2012a) (based on in situ hybridization (ISH) testing).

- 4.4 The submission proposed that pertuzumab be used in combination with trastuzumab and chemotherapy (Ptz+T+Chemo) for the adjuvant treatment of eBC in HER2 positive, lymph node positive patients.
- 4.5 The PBAC noted that the treatment landscape for this patient population with HER2-positive early breast cancer is quickly evolving, so it is difficult to determine the clinical place of pertuzumab in combination with trastuzumab, and it is unknown how this will impact on the presented financial forecasts. For example, the PBAC discussed that there is recent evidence which suggests that increasing the dose density of adjuvant chemotherapy results in fewer disease recurrences in breast cancer². Also, data presented at the June 2018 American Society of Clinical Oncology (ASCO) Annual Meeting suggested that 6 months of adjuvant treatment with trastuzumab was non-inferior to 12 months of treatment³. The PBAC also noted that neoadjuvant rather than adjuvant therapy is often undertaken, especially for high risk patients, and the benefits of adjuvant pertuzumab in these patients is unknown as they were not part of the APHINITY study population. The PBAC also noted that neratinib, a tyrosine kinase inhibitor that blocks HER2 signalling, is an emerging treatment option in HER2 positive eBC, and was approved by the FDA to be used after adjuvant therapy with trastuzumab and surgery⁴. The PBAC noted there is currently no data comparing neratinib and pertuzumab but anticipate potential impacts on pertuzumab's place in therapy.

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

5 Comparator

- 5.1 The submission nominated trastuzumab plus chemotherapy (T+Chemo) as the main comparator. The PBAC agreed with ESC and considered this was reasonable.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

² Gray R et al. (2017). Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials [abstract]. Cancer Res 2018;78(4 Suppl):Abstract nr GS1-01

³ Earl et al. ASCO ASM 2018, PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results. Abstract No. 506

⁴ US Food and Drug Administration (2017). FDA approves neratinib for extended adjuvant treatment of early stage HER2-positive breast cancer <https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm567259.htm>

Consumer comments

- 6.2 The PBAC noted and welcomed the input from an individual (1) and a health care professional (1) via the Consumer Comments facility on the PBS website. The comments described that pertuzumab used in combination with trastuzumab and chemotherapy is well tolerated. The comments also described that treatment with pertuzumab could prevent disease recurrence and that evidence has demonstrated that disease progression is reduced. The comments also noted that high risk patients with nodal involvement will benefit from pertuzumab treatment in combination with trastuzumab and chemotherapy.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the pertuzumab submission, on the basis of improved disease-free survival. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pertuzumab, which was A (out of A, B and C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies)⁵, based on a comparison with trastuzumab and chemotherapy.

Clinical trials

- 6.4 The submission is based on one head-to-head randomised trial comparing Ptz+T+Chemo (anthracycline or docetaxel plus carboplatin) to T+Chemo (anthracycline or docetaxel plus carboplatin) (N=4,804): APHINITY.
- 6.5 Table 3 presents the details of the trials presented in the submission.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
APHINITY (NCT01358877)	APHINITY Primary Clinical Study Report – BIG 4-11 / BO25126 / TOC4939g. Report No. 1075429. (Clinical Appendix)	July 2017
	von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer.	NEJM 2017; 377:122-131
	von Minckwitz. APHINITY trial (BIG 4-11): A randomised comparison of chemotherapy (C) plus trastuzumab (T) plus placebo (Pla) versus chemotherapy plus trastuzumab (T) plus pertuzumab (P) as adjuvant therapy in patients (pts) with HER2-positive early breast cancer (EBC).	Journal of Clinical Oncology. 2017;35(15)
	von Minckwitz G, Baselga J, Bradbury I et al. Adjuvant pertuzumab and herceptin in initial therapy of breast cancer: APHINITY (BIG 4-11/BO25126/TOC4939g).	Cancer Research. 2011; 71(24).

Source: Table 2.2.1, p43 of the submission.

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

⁵ Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, de Vries EGE, Piccart MJ: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Annals of Oncology* 26: 1547–1573, 2015

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Ptz + T + Chemo vs T + Chemo						
APHINITY	4,805	R, DB 45 mths	Low	HER2+ eBC	iDFS (primary outcome) OS, recurrence-free interval (RFI), distant RFI (DRFI), EORTC QLQ-C30 and EQ-5D-3L	iDFS used in economic model

DB=double blind; DRFI= distant recurrence free interval; EORTC=European organisation for research and treatment of cancer; iDFS=invasive disease-free survival; OS=overall survival; R=randomised; RFI=recurrence free interval; QLQ=quality of life questionnaire

Source: p44, p51, p52, p57 and p92 of the submission.

Comparative effectiveness

6.7 Table 5, Figure 1 and Figure 2 presents the results of the ITT analysis.

Table 5: Results of primary and secondary efficacy outcomes (ITT) at 3 years: time-to-event data

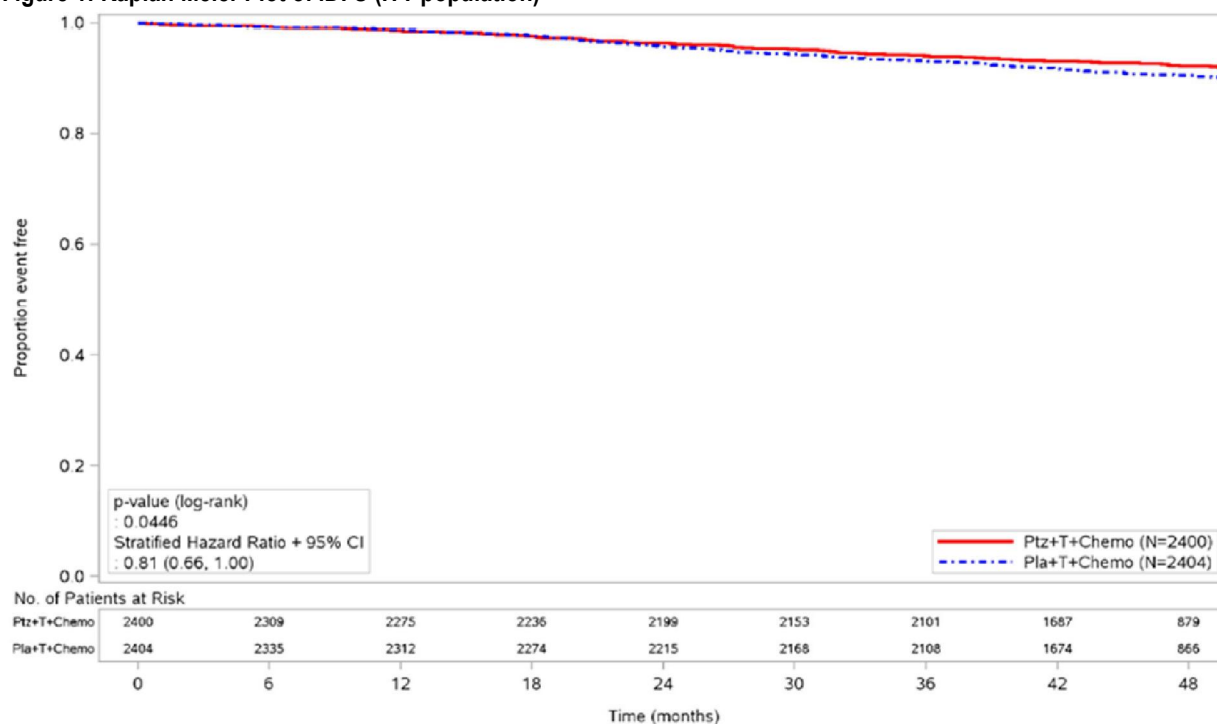
Outcome	Ptz+T+Chemo (N=2,400)		T+Chemo (N=2,404)		RD	P value (log rank test)	HR (95% CI)
	n/N with event (%)	Median time to event (95% CI)	n/N with event (%)	Median time to event (95% CI)			
Primary outcome							
iDFS	171/2,400 (7.1%)	NA	210/2,404 (8.7%)	NA	-1.6%	0.0446	0.81 (0.66, 1.00)
Secondary outcomes							
OS	80/2,400 (3.3%)	NA	89/2,404 (3.7%)	NA	-0.4%	0.4673	0.89 (0.66, 1.21)
RFI	138/2,400 (5.8%)	NA	173/2,404 (7.2%)	NA	-1.4%	0.0430	0.79 (0.63, 0.99)
DRFI	119/2,400 (5.0%)	NA	145/2,404 (6.0%)	NA	-1.1%	0.1007	0.82 (0.64, 1.04)

CI= confidence interval; DRFI= distant recurrence free interval; HR= Hazard Ratio iDFS= invasive disease-free survival; n= number of participants reporting data; N= total participants in group; OS= overall survival; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; RD= risk difference; RFI= recurrence free interval; T+Chemo= trastuzumab and chemotherapy.

Note: Bold indicates a statistically significant difference.

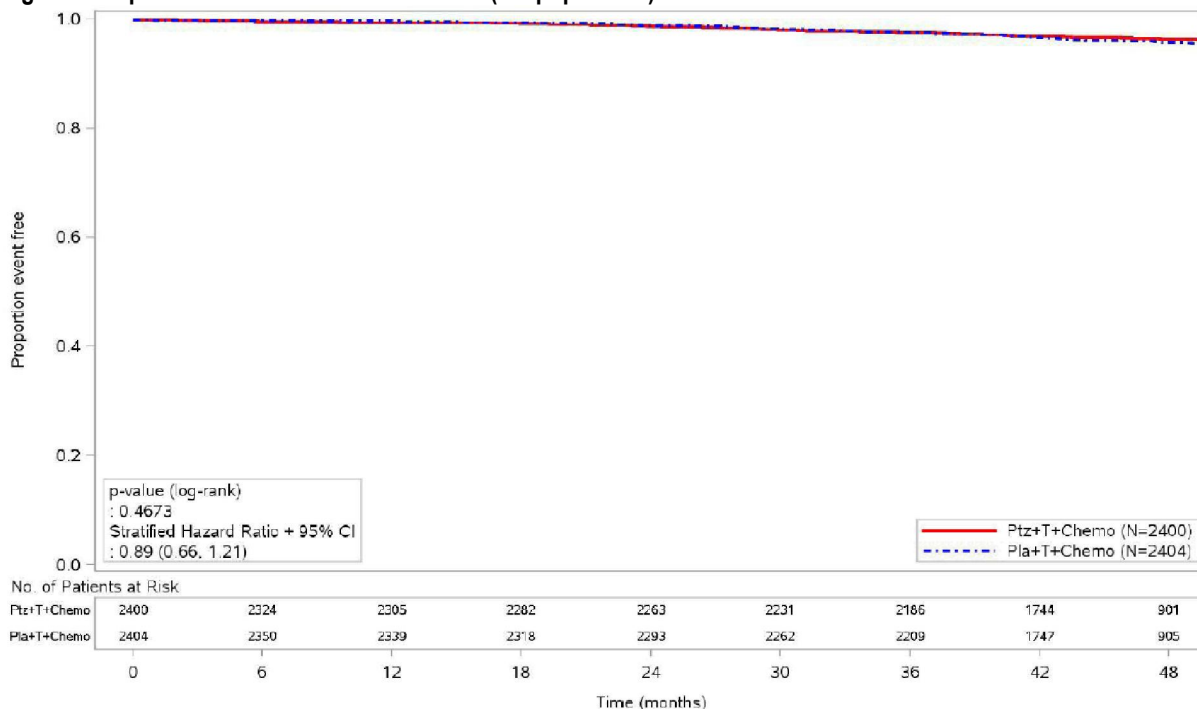
Source: Table 2.5.1, p61 of the submission and calculated during evaluation

Figure 1: Kaplan-Meier Plot of iDFS (ITT population)



CI =confidence interval; iDFS=invasive disease-free survival; ITT=intention to treat; Pla=placebo; Ptz=pertuzumab; T=trastuzumab
 Source: Figure 2.5.1, p62 of the submission

Figure 2: Kaplan-Meier Plot of Overall Survival (ITT population)



CI =confidence interval; ITT=intention to treat; Pla=placebo; Ptz=pertuzumab; T=trastuzumab
 Source: Figure 2.5.2, p62 of the submission

6.8 The submission also provided a subgroup analysis by lymph node status to align the trial population with the proposed PBS listing.

6.9 The submission claimed there was a plausible variation in treatment effect for lymph node positive patients on the basis of the following (p69 of the submission):

- Breast cancer with nodal involvement is more difficult to treat and reduces the chance of survival.
- Lymph node positive breast cancer is associated with early relapse and metastatic disease, as shown by (Lok 2017) where 78% of lymph node patients relapsed early, versus only 4% of lymph node negative patients.
- Hence, breast cancer patients with nodal involvement have a higher risk relapsing and of dying from their disease and represent a higher unmet clinical need (Nemoto 1980).

6.10 The TGA Clinical Evaluation Report noted that there was no indication from the APHINITY Clinical Study Report that the subgroup analyses were adjusted for multiplicity (TGA Clinical Evaluation Report).

6.11 The subgroup analysis was exploratory, but pre-specified and stratified at randomisation.

6.12 Table 6 presents the results of the subgroup analysis.

Table 6: Results of subgroup analysis with whole trial population results and complement results at 3 years: time-to-event data

Population	Ptz+T+Chemo n with event/N (%)	T+Chemo n with event/N (%)	Hazard ratio (95% CI)
iDFS (primary outcome)			
Whole trial population	171/2,400 (7.1%)	210/2,404 (8.7%)	0.81 (0.66, 1.00)
Identified subgroup (lymph node positive)	139/1,503 (9.2%)	181/1,502 (12.1%)	0.77 (0.62, 0.96)
Complement of subgroup (lymph node negative)	32/897 (3.6%)	29/902 (3.2%)	1.13 (0.68, 1.86)
Test for treatment effect variation	–	–	P = [redacted]
Overall survival (secondary outcome)			
Whole trial population	80/2,400 (3.3%)	89/2,404 (3.7%)	0.89 (0.66, 1.21)
Identified subgroup (lymph node positive)	[redacted]/1,503 ([redacted]%)	[redacted]/1,502 ([redacted]%)	[redacted] ([redacted], [redacted])
Complement of subgroup (lymph node negative)	[redacted]/897 ([redacted]%)	[redacted]/902 ([redacted]%)	[redacted] ([redacted], [redacted])
Test for treatment effect variation	–	–	P = [redacted]
RFI (secondary outcome)			
Whole trial population	138/2,400 (5.8%)	173/2,404 (7.2%)	0.79 (0.63, 0.99)
Identified subgroup (lymph node positive)	117/1,503 (7.8%)	153/1,502 (10.2%)	0.77 (0.60, 0.98)^c
Complement of subgroup (lymph node negative)	[redacted]/897 (2.3%)	[redacted]/902 ([redacted]%)	[redacted] ([redacted], [redacted]) ^d
Test for treatment effect variation	–	–	P = [redacted]
DRFI (secondary outcome)			
Whole trial population	119/2,400 (5.0%)	145/2,404 (6.0%)	0.82 (0.64, 1.04)
Identified subgroup (lymph node positive)	[redacted]/1,503 ([redacted]%)	[redacted]/1,502 ([redacted]%)	[redacted] ([redacted], [redacted])
Complement of subgroup (lymph node negative)	[redacted]/897 ([redacted]%)	[redacted]/902 ([redacted]%)	[redacted] ([redacted], [redacted])
Test for treatment effect variation	–	–	P = [redacted]

CI= confidence interval; DRFI= distant recurrence free interval; iDFS= invasive disease-free survival; n= number of participants reporting data; N= total participants in group; OS= overall survival; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; RFI= recurrence free interval; T+Chemo= trastuzumab and chemotherapy.

Note: Bold indicates a statistically significant difference.

Source: Table 2.6.1, p70 of the submission

6.13 The APHINITY trial follow up remains ongoing. Based on the available data, there was a 23% reduction in risk of recurrence or death (HR=0.77, 95% CI [0.62, 0.96]).

The iDFS event-free rates were 91.99% vs. 90.15% at 3 years (difference of 1.84%) and 89.88% vs. 86.68% at 4 years (difference of 3.2%), for Ptz+H+Chemo versus H+Chemo, respectively. The ESC noted the difference at 4 years is larger than that at 3 years. Future follow up reporting dates are indicated for late 2019, 2022 and the final report expected in 2026.

- 6.14 EORTC QLQ-C30: The mean global health status scores showed a clinically meaningful worsening from the baseline mean score (72.9 in Ptz+T+Chemo vs. 72.5 T+Chemo) at the end of taxane treatment (Week 13) (█████ in Ptz+T+Chemo vs. █████ T+Chemo) and returned to baseline thereafter in both arms (APHINITY BO25126a Clinical Study Report).
- 6.15 EQ-5D: There were no major differences (≥ 5 percentage points) between treatment arms in the five EQ-5D domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

Comparative harms

- 6.16 Table 7 presents a summary of patient-relevant harms, based on the APHINITY trial.

Table 7: Summary of key adverse events in the randomised trial in the ITT analysis

Trial ID	Ptz+T+Chemo n with event/N (%)	T+Chemo n with event/N (%)	RR (95% CI)
Any AE ^a	2361/2364 (99.9%)	2393/2405 (99.5%)	1.004 (1.001, 1.007)
Grade ≥ 3 AE	1518/2364 (64.2%)	1379/2405 (57.3%)	1.120 (1.070, 1.172)
SAE	692/2364 (29.3%)	585/2405 (24.3%)	1.203 (1.095, 1.322)
AEs leading to treatment discontinuation	309/2364 (13.1%)	277/2405 (11.5%)	1.135 (0.975, 1.321)
AEs leading to dose modification/interruption	1217/2364 (51.5%)	1064/2405 (44.2%)	1.164 (1.096, 1.235)
Treatment-related AEs (HER2 targeted)	█████/2364 (█████%)	█████/2405 (█████%)	█████ (█████, █████)
AEs leading to death	10/2364 (0.4%)	14/2405 (0.6%)	0.727 (0.323, 1.633)
Total deaths	73/2364 (3.1%)	95/2405 (4.0%)	0.782 (0.579, 1.055)
Treatment-related deaths	1/2364 (0.0)%	1/2405 (0.0%)	1.017 (0.064, 16.256)

AE= adverse event; CI= confidence interval; n= number of participants reporting data; N= total participants in group; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; SAE= serious adverse event; T+Chemo= trastuzumab and chemotherapy.

Note: Bold indicates a statistically significant difference.

Source: Table 2.5.2, p64 of the submission

- 6.17 In the APHINITY trial almost all patients in both treatment arms experienced at least one adverse event (AE). A higher proportion of patients in the Ptz+T+Chemo arm experienced one or more grade ≥ 3 AEs, serious adverse events (SAEs), AEs leading to dose modification/interruption of any study treatment and AEs considered related to study treatment compared to the T+Chemo arm.

- 6.18 The most common AEs ($\geq 30\%$ in either treatment arm) that were significantly more common in the Ptz+T+Chemo arm were diarrhoea (71.2% vs. 45.2% in the

Ptz+T+Chemo and T+Chemo arms, respectively), nausea (69.0% vs. 65.5%), and fatigue (48.8% vs. 44.3%).

- 6.19 Patients were more likely to experience grade ≥ 3 AEs relating to diarrhoea (RR=3.924, 95%CI: 2.600, 5.923) and SAEs relating to diarrhoea (RR=3.278, 95%CI: 1.938, 5.546).
- 6.20 The submission stated the full set of safety and QoL data for the lymph node positive subgroup were not presented in the submission as there is no clinically plausible reason for this subgroup of patients to have a different safety profile and QoL compared with the ITT population. The treatment related grade 3-5 adverse events in the lymph node positive subgroup was summarised in the submission, for example total number of patients with at least one adverse event was [REDACTED]% vs. [REDACTED]% in the Ptz+T+Chemo and T+Chemo arms, respectively, with a relative risk (95% CI) of [REDACTED] ([REDACTED], [REDACTED]). (p71 of submission). For the ITT population, total number of patients with at least one adverse event was [REDACTED]% vs. [REDACTED]% in the Ptz+T+Chemo and T+Chemo arms, respectively, with a relative risk (95% CI) of [REDACTED] ([REDACTED], [REDACTED]).

Benefits/harms

- 6.21 A summary of the comparative benefits and harms for Ptz+T+Chemo versus T+Chemo in whole trial population and lymph node positive patients is presented in Table 8.

Table 8: Summary of comparative benefits and harms for Ptz+T+Chemo and T+Chemo in whole trial population and lymph node positive patients

Time-to-event outcome: APHINITY						
	Ptz+T+Chemo	T+Chemo	Absolute difference	HR (95% CI)		
iDFS (whole trial population)						
Recurrence, n/N (%)	171/2,400 (7.1%)	210/2,404 (8.7%)	-	0.81 (0.66, 1.00)		
Median iDFS (months)	NA	NA	NA			
iDFS at 3 years, % (95% CI)	94.1% (93.1, 95.0)	93.2% (92.2, 94.3)	0.9%			
iDFS (lymph node positive patients)						
Recurrence, n/N (%)	139/1,503 (9.2%)	181/1,502 (12.1%)	-	0.77 (0.62, 0.96)		
Median iDFS (months)	NA	NA	NA			
iDFS at 3 years, % (95% CI)	92.0% (90.6, 93.4)	90.2% (88.6, 91.7)	1.8%			
OS (whole trial population)						
Deaths n/N (%)	80/2,400 (3.3%)	89/2,404 (3.7%)	-	0.89 (0.66, 1.21)		
Median (months)	NA	NA	NA			
OS at 3 years, % (95% CI)	97.7% (97.0, 98.3)	97.7% (97.1, 98.3)	0.0			
OS (lymph node positive patients)						
Deaths n/N (%)	█/1,503 (█%)	█/1,502 (█%)	-	█ (█, █)		
Median (months)	█	█	█			
OS at 3 years, % (95% CI)	█	█	█			
Harms (whole trial population)						
	Ptz+T+Chemo n/N	T+Chemo n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Ptz+T+Chemo	T+Chemo	
Grade ≥3 AE						
APHINITY	1518/2364 (64.2%)	1379/2405 (57.3%)	1.12 (1.07, 1.172)	64.2	57.3	6.9% (4.1%, 9.6%)
SAE						
APHINITY	692/2364 (29.3%)	585/2405 (24.3%)	1.203 (1.095, 1.322)	29.3	24.3	4.9% (2.4%, 7.5%)
Grade ≥3 AE diarrhoea						
APHINITY	108/2364 (4.6%)	28/2405 (1.2%)	3.924 (2.6, 5.923)	4.6	1.2	3.4% (2.5%, 4.3%)
SAE diarrhoea						
APHINITY	58/2364 (2.5%)	18/2405 (0.7%)	3.278 (1.938, 5.546)	2.5	0.7	1.7% (1.0%, 2.4%)

* Median duration of follow-up: APHINITY = 45 months

AE= Adverse event; CI= confidence interval; HR= hazard ratio; iDFS= invasive disease free survival; OS= overall survival; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; RD= risk difference; RR= relative risk; SAE= serious adverse event; T+Chemo= trastuzumab and chemotherapy; NA= not available; NR= not reported

Source: Table 2.5.1, p61, Table 2.5.2, p64, Table 2.5.4 p67, Table 2.5.5 p68, and Table 2.6.1 p70 of the submission, the CSR and calculated during the evaluation.

6.22 On the basis of direct evidence presented by the submission, for every 100 patients, with involvement of ≥1 positive lymph nodes, treated with Ptz+T+Chemo in comparison to T+Chemo:

- At 3 years:
 - Approximately 2 additional patients would not experience recurrence (in terms of iDFS, the time a patient lives without return of invasive disease).
 - No difference in overall survival.
- Over a median duration of follow-up of 45 months:
 - Approximately 7 additional patients would experience a grade ≥3 AE.
 - Approximately 5 additional patients would experience a SAE.

- Approximately 3 additional patients would experience grade ≥ 3 AE diarrhoea.
- Approximately 2 additional patients would experience SAE diarrhoea.

Clinical claim

- 6.23 The submission described Ptz+T+Chemo as superior in terms of effectiveness compared with T+Chemo in patients with HER2 positive, lymph node positive eBC.
- 6.24 The PBAC considered that the claim of superior comparative effectiveness was reasonable but questioned whether the modest benefit demonstrated in the trial was clinically meaningful. The PBAC noted the reduction in disease recurrence in the ITT population was statistically significant (iDFS HR=0.81, P=0.0446). However, the PBAC agreed with the ESC's view that while the HR was statistically significant, the absolute benefit at 3 years was small (-0.9%).
- 6.25 The submission proposed a PBS restriction which would restrict treatment to lymph node positive patients. The ESC noted the reduction in disease recurrence was larger in lymph node positive patients (iDFS HR=0.77, 95%CI: 0.62, 0.96, P=not reported) and the impact was not statistically significant in lymph node negative patients (iDFS HR=1.13, 95%CI: 0.68, 1.86, P=not reported). However, the test for treatment effect variation was not statistically significant (P=0.1688). The PBAC agreed with the ESC's view that the non-significant result for this test may be due to lack of power given that less than 4% of lymph node negative patients had a iDFS event. The PBAC, based on the current evidence, considered that treatment should be limited to lymph node positive patients as proposed in the submission's restriction and the likely registration of pertuzumab on the ARTG.
- 6.26 The submission described Ptz+T+Chemo as inferior in terms of safety compared to T+Chemo. The PBAC considered that this was reasonable and was supported by the data.
- 6.27 The ESC noted that the advisors attending the Roche eBC advisory board meeting in August 2017 stated that any treatment with a hazard ratio of 0.8 or less was clinically meaningful and worth adopting into standard clinical practice. The submission stated that an improvement in DFS alone measured with a hazard ratio with a lower limit 95% confidence interval between 0.65 and 0.8 is considered a grade of clinical benefit that represents substantial improvement, based on ESMO-MCBS version 1.0 (published in 2015). In 2017, version 1.1 was published⁶. Recently published recommendations in the American Society of Clinical Oncology (ASCO) Guidelines state 'Clinicians may add 1 year of adjuvant pertuzumab to trastuzumab-based combination chemotherapy in patients with high-risk, early-stage, HER2-positive breast cancer'⁷. The PBAC noted the

⁶ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

⁷ Denduluri N et al, Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO

submission was consistent with the ASCO guidelines, but its concerns about the place in therapy remains (see Section 4 Population and Disease).

6.28 The PBAC had concerns regarding the applicability of the trial data presented in the submission and its use on the PBS:

- The PBAC noted in the APHINITY trial, the majority of patients were hormone receptor positive (HR+, approximately 64%), which the submission demonstrated was consistent to the market research of Australian HER2 positive eBC patients ([REDACTED] %). [REDACTED]. However, the PBAC noted the hormone receptor status potentially impacted on the efficacy of pertuzumab with a greater reduction in recurrence in HR- patients (HR =0.76, 95% CI 0.56, 1.04 versus HR =0.86, 95% CI 0.66, 1.13 for HR+ patients). The PBAC considered that the comparative benefit of adding pertuzumab to the treatment of the subgroup of patients who were lymph node positive and HR+ was unknown. The PBAC considered it would have been informative to know the outcomes from this subgroup, as it represents a large group of patients who would seek PBS treatment.
- The PBAC noted the cardiac concerns with pertuzumab and considered this to be an important consideration in the adjuvant setting. The PBAC considered that there may be higher rates of HF and CM in the Australian population than seen in the trial.
- The PBAC noted other changes to the treatment of adjuvant BC, such as use of dose dense regimens, use of neo-adjuvant therapy and shorter durations of trastuzumab (see paragraph 4.5 above) may further limit the applicability of the trial results.

6.29 Overall, the PBAC was concerned that the modest benefit of adding pertuzumab to trastuzumab and chemotherapy was outweighed by the increased risk of AEs (in particular the cardiac risks and significant difference in experiencing diarrhoea), the uncertain magnitude of benefit in the HR+ lymph node positive patients and the uncertain place in therapy.

Economic analysis

6.30 The submission presented a stepped economic evaluation which compared Ptz+T+Chemo with T+Chemo, based on the APHINITY trial as well as external data sources and implemented a modelled evaluation. The type of economic evaluation presented was a cost-utility analysis.

6.31 Table 9 summarises the key components of the economic evaluation.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	50 years in the model base case versus 45 months in the APHINITY trial
Outcomes	LYG and QALYs gained
Methods used to generate results	Markov model
Health states	<p>iDFS, Locoregional Recurrence, Remission, Distant Recurrence (1st line mBC), Distant Recurrence (2nd line mBC), Death</p> <p>Distant Recurrence (1st line mBC) consists of two health states: Distant Recurrence (1st line mBC, early progressors) and Distant Recurrence (1st line mBC, late progressors).</p> <p>Distant Recurrence (2nd line mBC) consists of two health states: Distant Recurrence (2nd line mBC, early progressors) and Distant Recurrence (2nd line mBC, late progressors).</p> <p>The ESC considered that the model structure was appropriate.</p>
Cycle length	1 week
Transition probabilities	<p>iDFS to locoregional recurrence or the distant recurrence health states: APHINITY trial iDFS Kaplan-Meier data extrapolated from 45 month (median follow up time) to lifetime (50 years) by fitting the log-logistic parametric functions to the APHINITY data. APHINITY trial data was based on the lymph node positive subgroup, not the ITT population. Thus, the impact on the ICER of limiting access to lymph node positive subgroup (compared to the ITT population) was not assessed in the submission. Further discussion below. The submission fitted separate parametric functions to each treatment arm (rather than fitting a single parametric function and using an interaction term to indicate whether the patient received pertuzumab). This approach was not justified by the submission. The ESC noted that using the function that performs best under AIC criteria for both arms would increase the ICER. Further discussion below.</p> <p>The extrapolation of iDFS data started from the median follow up of the APHINITY trial (45 month). No justification was provided for why iDFS was extrapolated from the median of follow up rather than a later time point. The submission conducted a sensitivity analysis by extrapolating the data at the end of follow up, which increased the ICER by \$10,000/QALY.</p> <p>The locoregional recurrence health state is a tunnel state where patients reside in this state for up to 12 month if they do not experience death. This is reasonable.</p> <p>Remission to Distant recurrence (1st line mBC): single transition probability per cycle derived from Hamilton et al 2015. The Hamilton study analysed retrospective data sets collected during 1989 to 2005 from four different centres. The ESC notes that the historical rate of distant recurrence from remission may have changed since this study due to changes in treatment patterns.</p> <p>Early progressors were defined as patients progressing within 18 months after initial treatment. This is reasonable.</p> <p>Distant recurrence (1st line mBC, early progressors) to (2nd line mBC, early progressors) and death: -Single transition probability per cycle based on EMILIA trial (trastuzumab emtansine arm). Distant recurrence (1st line mBC, late progressors) to (2nd line mBC, late progressors) and death: single transition probability per cycle based on CLEOPATRA trial. The EMILIA and CLEOPATRA trials were previously considered by the PBAC for the PBS listing of trastuzumab emtansine⁸ and pertuzumab⁹ for mBC, respectively. This is reasonable, although it is unknown whether the use of pertuzumab for eBC will reduce the effectiveness of pertuzumab for mBC.</p> <p>The trial results were applied using a single transition probability based on an exponential function, rather than applying the Kaplan-Meier data and extrapolated using a parametric function. Of note, in the previous PBAC submissions for mBC, a gamma function was fitted to both EMILIA and</p>

⁸ PBAC (March 2014) Public Summary Document - Trastuzumab emtansine, injections, 100 mg vial and 160 mg vial, Kadcyca®, Roche Products Pty Ltd

⁹ PBAC (March 2014) Public Summary Document– Pertuzumab, 420 mg/14 mL injection, 1 x 14 mL vial Perjeta®, Roche Products Pty Ltd

Component	Summary
	<p>CLEOPATRA trials. Using different parametric functions (except Weibull function) had limited impact on the ICERs for both drugs. Using an exponential function simplifies the model, especially for the mBC setting. However, exponential parametric function may not be the best fit for the Kaplan-Meier curve and may lead to biased results. The direction of bias is unknown. Further discussion below.</p> <p>Transition probabilities from iDFS, locoregional recurrence, remission to death were based on a single transition probability based on mortality data from the APHINITY trial and background mortality (whichever is higher). From age 51 to 61, the death rate was constant and based on the mortality data from the APHINITY trial. At age 62, the background mortality rate became higher than the APHINITY trial death rate, so from age 62 onwards, the death rate was based on the background mortality rate which increased steadily. This is reasonable.</p> <p>It was assumed that the treatment effect decreases linearly from year ■ to year ■. There was no treatment effect after year ■. Applying time limited treatment effect is appropriate, but whether the treatment effect could last over ■ years is unknown and introduces uncertainty. Of note, for the T+Chemo 2006 PBAC submission¹⁰, the PBAC recommended that treatment effect for trastuzumab should be null after year 5. A sensitivity analysis of the treatment effect being null after 5 years was conducted and the ICER is highly sensitivity to the duration of the treatment effect. Further discussion below.</p>
Utilities	<p>iDFS (on treatment), iDFS (off treatment), locoregional recurrence and remission health states used EQ-5D-3L data from the APHINITY trial and valued using the Australian weights for the general population estimated by Viney et al. (2011).</p> <p>Distant recurrence: Lloyd 2006 2nd line mBC: Lloyd 2006</p> <p>These are reasonable.</p>

iDFS= Invasive disease free survival; LYG= life years gained; mBC: metastatic breast cancer; QALYs= Quality adjusted life years. Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; T+Chemo= trastuzumab and chemotherapy
Source: Table 3.1.2, p82 of the submission and compiled during the evaluation.

6.32 Table 10 presents the key drivers of the economic model.

¹⁰ PBAC (October 2006) Public Summary Document – Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin®, Roche Products Pty Ltd

Table 10: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Extrapolation of immature trial data to 50 years substantially increases the uncertainty in the ICER	High
	Treatment effect started to decrease after █ years and no more treatment effect after █ years.	High
	Extrapolation of APHINITY using a log-logistic function	Moderate
	Extrapolation of EMILIA and CLEOPATRA trial using an exponential function	Unclear
Price of pertuzumab	A discount of █% on the ex-manufacturer price of trastuzumab was applied in the base case, which the submission stated is required in order to achieve a cost-effective ICER.	High

ICER= Incremental cost-effectiveness ratio; ITT: Intent-to-treat

Source: compiled during the evaluation

6.33 Table 11 shows the results of the stepped analysis. The submission did not present an analysis of the cost-effectiveness of Ptz+T+Chemo in the ITT population compared to lymph node positive patients only. The PSCR stated it is irrelevant to assess the cost-effectiveness in the ITT population as this is not being sought for reimbursement. The ESC noted, while listing is proposed in the subgroup, without the ICER for the ITT population it was not possible to assess the impact on the cost-effectiveness of use in the broader population compared with the subgroup.

Table 11: Results of the stepped economic evaluation

Step and component	Ptz+T+Chemo	T+Chemo	Increment	Increment with [REDACTED] % price discount (step 8 in submission)	Increment with [REDACTED] % price discount (step 9 in submission)
Step 1: trial-based costs and outcomes					
Costs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant
Incremental cost/extra QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant
Step 2: parametric extrapolation from 45 months over lifetime horizon					
Costs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant
Incremental cost/extra QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant
Step 3 (application of time limited treatment effect)					
Costs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant
Incremental cost/extra QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant
Step 4 (incorporation of MRU costs)					
Costs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant
Incremental cost/extra QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant
Step 5 (incorporation of AE related costs)					
Costs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant
Incremental cost/extra QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Dominant
Step 6 (incorporation of utility values for QALYs) – included in steps above					
Step 7 (inclusion of end of life costs)					
Costs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALYG	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

AE= adverse event; ICER= Incremental cost-effectiveness ratio; LYG= Life years gained; MRU= medical resource use; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; QALYG= Quality adjusted life years gained; RSA= Risk share agreement; T+Chemo= trastuzumab and chemotherapy.

Source: Table 3.8.1, Table 3.8.2, Table 3.8.3, Table 3.8.4, Table 3.8.5, Table 3.8.6 and Table 3.8.7, p108- p111 of the submission.

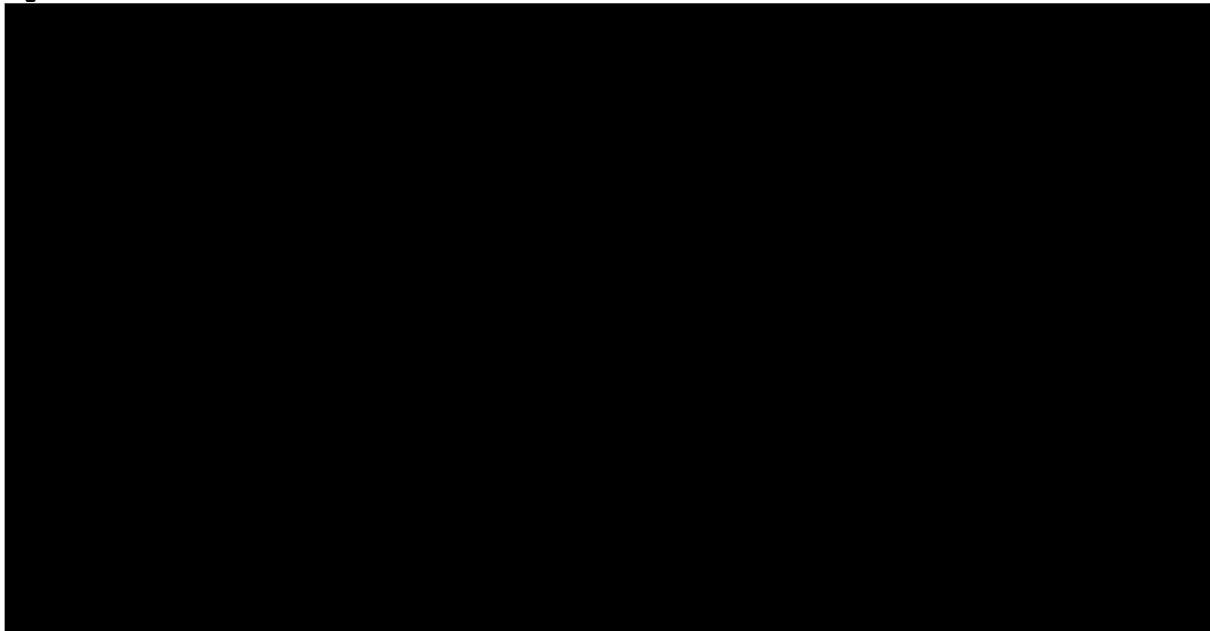
The redacted table shows ICERs in the range of dominant to more than \$200,000/QALY or Life year gained.

6.34 Steps 1 to 6 as presented in the submission did not apply the proposed special pricing discount to trastuzumab in the Ptz+T+Chemo arm. In Step 2, the model included the Kaplan-Meier data (up to 45 months), which were extrapolated to a life time horizon (50 years). This had a significant impact on the ICER.

6.35 In Step 8, a price discount of [REDACTED] % was applied to [REDACTED] in the Ptz+T+Chemo arm to achieve an ICER of \$45,000/QALY – \$75,000/QALY gained.

- 6.36 In Step 9, a price discount of [REDACTED]% was applied to [REDACTED] in the Ptz+T+Chemo arm and the ICER became dominant.
- 6.37 The ESC noted that the values presented in the table above would be impacted in Step 1 to 8 due to the recent statutory price reduction.
- 6.38 Figure 3 shows the Markov traces for iDFS, progression and OS curves for the Kaplan-Meier data (within the 45 months) and extrapolated to 50 years.

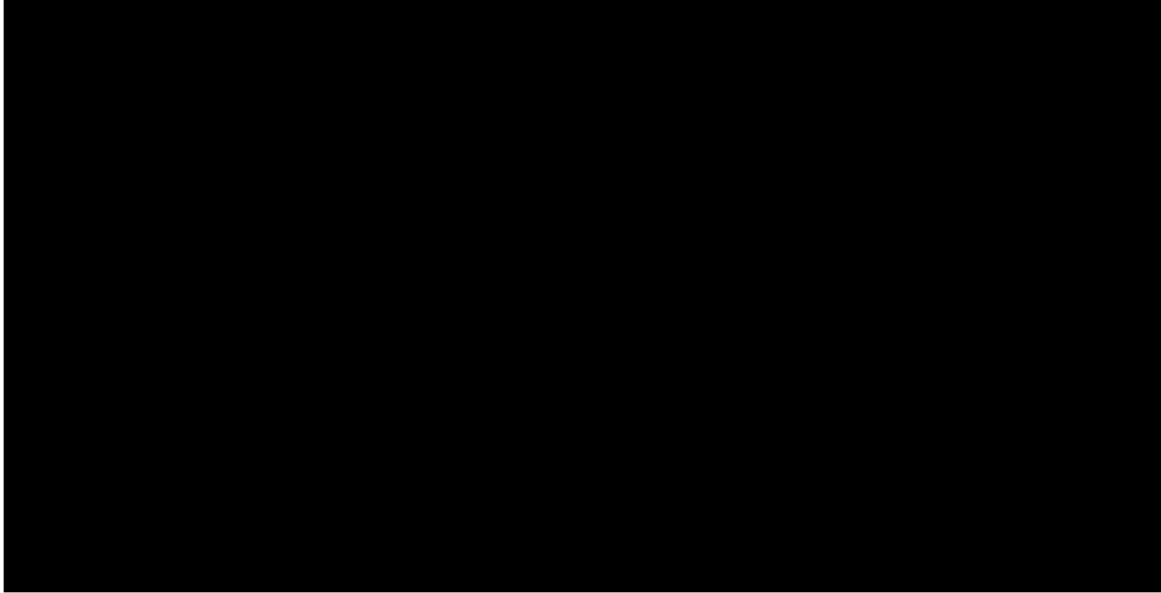
Figure 3: Markov traces for Ptz+T+Chemo and T+Chemo survival curves



Source: Figure 3.7.3, p107 of the submission

- 6.39 When inspecting the Markov traces for iDFS, progression and OS, the ESC noted that nearly all of the benefit was from the extrapolated portion of the curves, and that a substantial proportion of the gain in overall survival was for the period post 84 months, the time point at which the [REDACTED]. The ESC noted, consistent with this, the model results were sensitive to the time horizon (see below).
- 6.40 Figure 4 and Figure 5 show the Markov traces of all health states for both arms. The health states include iDFS, locoregional recurrence, remission, distant recurrence (1st line mBC early progressors and late progressors), 2nd line mBC (early progressors and late progressors) and death.

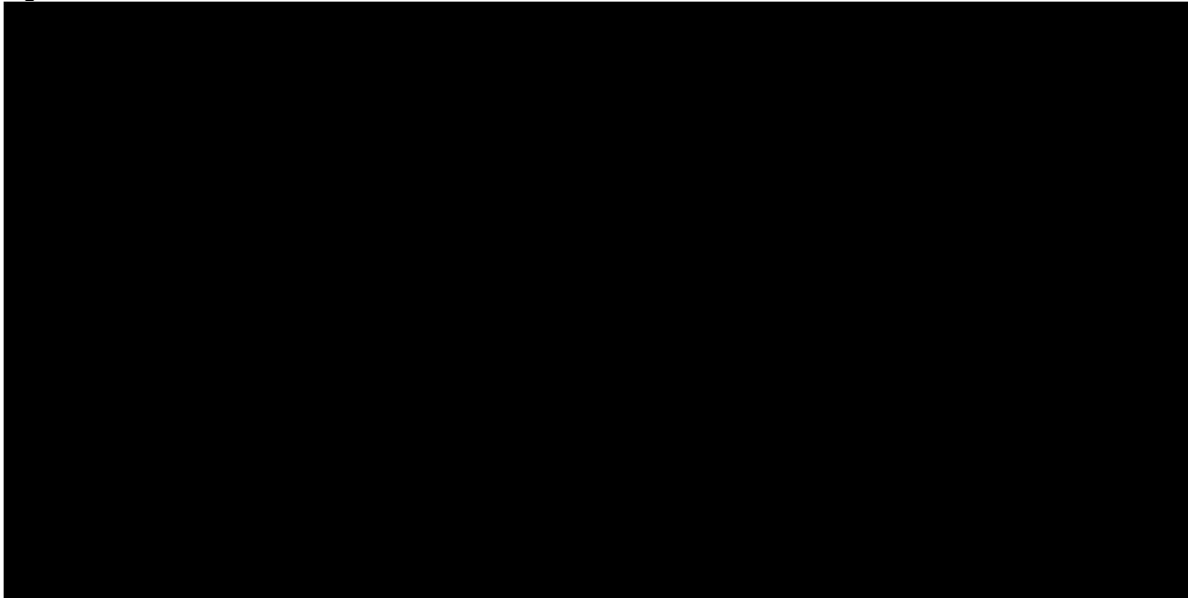
Figure 4: Markov traces of all health states for Ptz+T+Chemo



iDFS= invasive disease free survival; mBC= metastatic breast cancer; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; T+Chemo= trastuzumab and chemotherapy.

Source: prepared during the evaluation based on sheet PH of Economic Evaluation.xlsx

Figure 5: Markov traces of all health states for T+Chemo



iDFS= invasive disease free survival; mBC= metastatic breast cancer; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; T+Chemo= trastuzumab and chemotherapy.

Source: Prepared during the evaluation based on sheet H of Economic Evaluation.xlsx

6.41 The submission performed univariate sensitivity analyses and the results are summarised in Table 12.

Table 12: Results of sensitivity analyses

Univariate sensitivity analyses	Incremental cost	Incremental QALY	ICER
Base case	████████	████████	████████
Discount rate (base case 5% costs and outcomes)			
0% costs and outcomes	████████	████████	████████
3.5% costs and outcomes	████████	████████	████████
Time horizon (base case 50 years)			
5 years*	████████	████████	████████
10 years*	████████	████████	████████
20 years*	████████	████████	████████
45 years	████████	████████	████████
55 years	████████	████████	████████
Extrapolation (base case log-logistic extrapolation)			
Weibull	████████	████████	████████
Exponential	████████	████████	████████
Log normal	████████	████████	████████
Gamma	████████	████████	████████
Gompertz	████████	████████	████████
Treatment effect (base case treatment effect decrease from █ years null from █ years)			
Treatment effect decrease from █ years null from █ years	████████	████████	████████
Treatment effect null after 5 years (based on previous PBAC recommendations for the T+Chemo 2006 PBAC submission**)*	████████	████████	████████
Extrapolation (base case from median follow up 45 month)			
Extrapolate from the end of follow up (█ month)	████████	████████	████████
eBC utility (base case: APHINITY pooled data)			
Rautalin 2017	████████	████████	████████
Hedden 2012	████████	████████	████████
Lidgren 2007	████████	████████	████████
mBC utility (base case: Lloyd 2006)			
Rautalin 2017	████████	████████	████████
Hedden 2012	████████	████████	████████
Lidgren 2007	████████	████████	████████
Paracha 2017	████████	████████	████████
Lambert 2016	████████	████████	████████
Cure (base case proportion cured: █%)			
Maximum cure proportion: █%, cure proportion starts to increase at █ months, maximum cure proportion reached at █ months	████████	████████	████████

*Sensitivity analysis conducted during the evaluation.

**PBAC (October 2006) Public Summary Document – Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin®, Roche Products Pty Ltd

Source: prepared during the evaluation based on figure 3.9.3, p115 of the submission and different drop down options provided in the Economic Evaluation.xlsx.

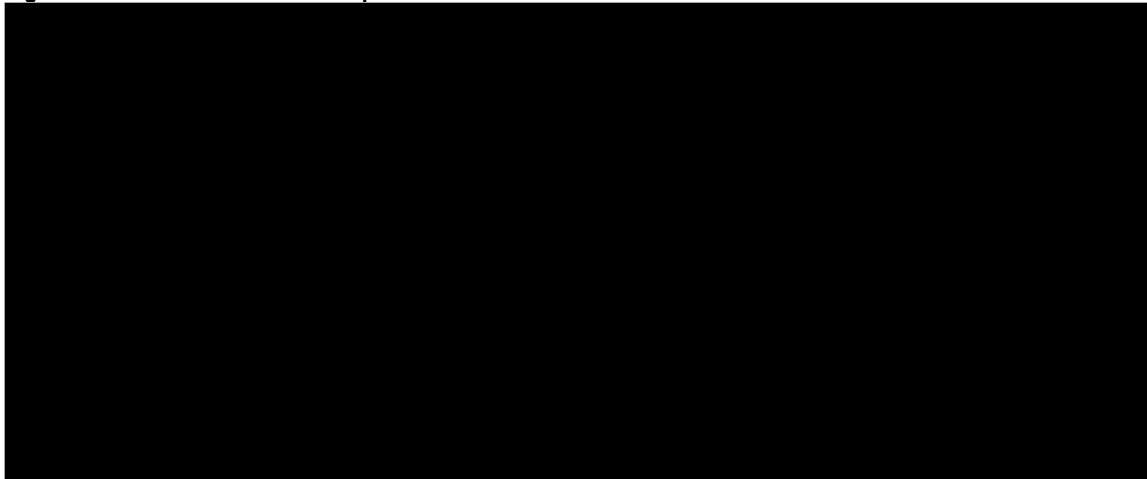
The redacted table shows ICERs in the range of \$15,000/QALY to more than \$200,000/QALY.

6.42 Overall the ICER was most sensitive to the time horizon and the duration of the treatment effect. Additional sensitivity analyses were tested during the evaluation and only had a minimal impact on the ICER.

6.43 Figure 6 shows that with a time horizon of five years, the incremental cost per QALY gained (ICER) is \$ more than \$200,000. At 10 years, the ICER is more than \$200,000, whereas at 50 years, the ICER decreases significantly to \$45,000/QALY – \$75,000/QALY (base case). The ESC noted there was no statistically significant difference in the overall survival (OS) between the two trial arms within the

APHINITY trial (up to 45 months follow up). However, the model (extrapolated to 50 years) generated [REDACTED] life years gained with Ptz+T+Chemo compared with T+Chemo. The estimated life years gained increases as the time horizon increases, and the incremental cost-effectiveness ratio (ICER) is highly sensitive to the time horizon. The PSCR argued the model appropriately models 50 years as the (lifetime) time horizon. Noting the 2006 PBAC recommendation of T+Chemo was based on a model with a 40 year time horizon, the PSCR states since then, the standard of care and clinical management of breast cancer has evolved, such as the treatments for metastatic breast cancer (mBC). While the PBAC agreed that standard of care has improved since 2006, the PBAC considered that use of the 50-year time horizon was overly high and reduced the reliability of the ICERs given the available trial follow-up and that there was no difference in OS.

Figure 6: APHINITY trial data extrapolated to different time horizon VS ICER results

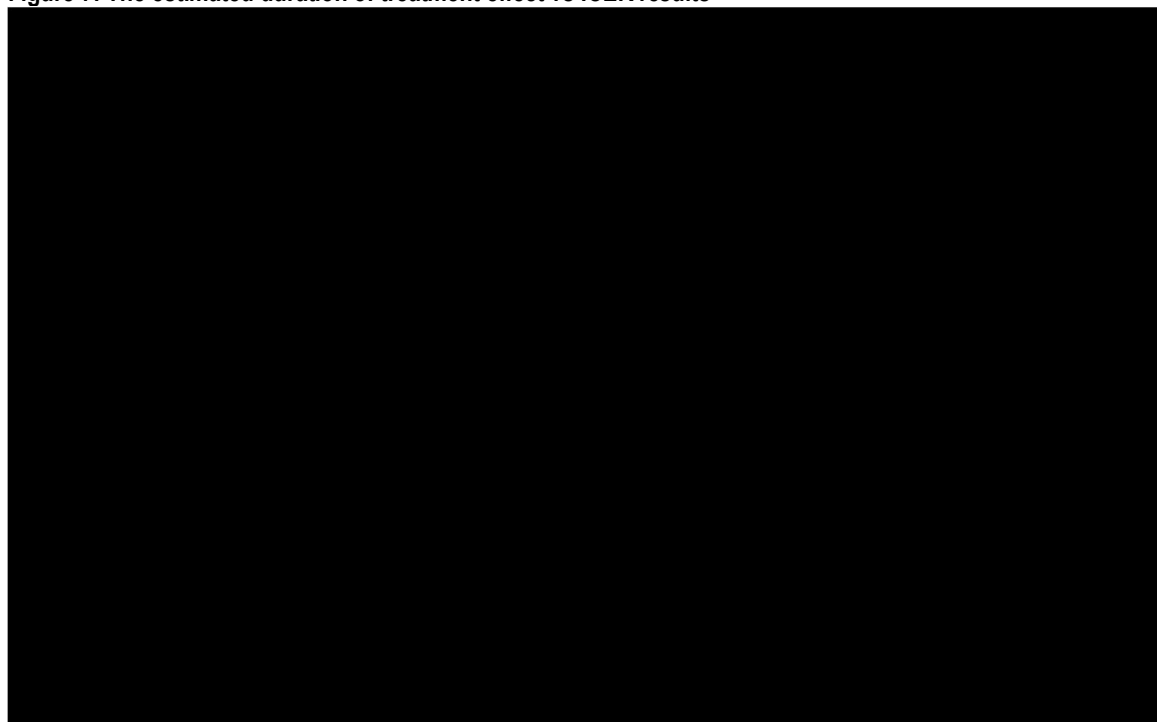


ICER = incremental cost-effectiveness ratio
Source: conducted during the evaluation

6.44 Figure 7 shows the effect of the estimated duration of treatment effect on the ICER. The ICER is estimated to be \$105,000/QALY – \$200,000 with the treatment effect being null after five years (i.e. 100% duration effect at 5 years and then 0% immediately after this time point), and \$45,000/QALY – \$75,000 with the treatment effect being reduced from [REDACTED] years and null after [REDACTED] years (base-case). Applying a time limited treatment effect is appropriate, but whether the treatment effect could be maintained over [REDACTED] years is unknown and introduces uncertainty. For the 2006 PBAC submission for trastuzumab for early breast cancer (eBC) the PBAC recommended that treatment effect for trastuzumab should be null after year five. The PSCR argued that new studies based on long term data from the HERA (Cameron 2017) and BCIRG006 (Slamon 2015) trials have shown that the incremental effect of H+Chemo is maintained over a 10 year period, despite a treatment duration of one year. Therefore, the sponsor considers it reasonable to assume that the treatment effect associated with one year of Ptz+H+Chemo treatment over H+Chemo as measured in the APHINITY trial will last for [REDACTED] years (PSCR). The ESC noted the evidence presented in the submission asserting that the treatment effect may endure beyond five years. However, the ESC considered that there was uncertainty around the duration of benefit and noted the ICER was highly sensitive to this.

The PBAC agreed with the ESC’s view and also noted the clinical evidence indicated modest benefits.

Figure 7: The estimated duration of treatment effect vs ICER results



The formula in the model was modified so that before the cut-off point the duration effect is 100%, and after it is 0%. So in effect waning is completely removed.

ICER = incremental cost-effectiveness ratio

Source: conducted during the evaluation.

6.45 The ESC noted the submission stated that the best fitting model (the log logistic model) was selected using the Akaike Information Criterion (AIC), visual inspection of model fit to the Kaplan-Meier data. Table 13 presents the AIC from both treatment arms and the pooled results for different parametric functions. The ESC considered selection of the log-logistic function based on the pooled (summed) AIC, which forces common functional form, was not adequately justified in the submission. The PBAC agreed with the ESC’s view and further noted that the application of the log-logistic function resulted in a lower ICER compared to the other parametric functions.

Table 13: Akaike Information Criterion (AIC)

Extrapolation function	AIC		
	Ptz+T+Chemo	T+Chemo	Pooled
Weibull			
Exponential			
Log-logistic (applied in submission)			
Log-normal			
Gamma			
Gompertz			

Source: Prepared during the evaluation

6.46 The rates of progression in the metastatic breast cancer (mBC) health states were based on the EMILIA and CLEOPATRA trials, which were previously considered by the PBAC for the PBS listing of trastuzumab emtansine and pertuzumab for mBC, respectively. The ESC considered this was reasonable,

although it is unknown whether the use of pertuzumab for eBC will reduce the effectiveness of pertuzumab for mBC. The PSCR stated that the effectiveness of pertuzumab for mBC was considered to remain effective following prior use in eBC, based on the mechanism of action of HER2-targeted agents. Non-clinical studies have revealed that the anti-tumour activity of pertuzumab and trastuzumab do not lead to loss of HER2 expression on tumour cells.

- 6.47 The EMILIA and CLEOPATRA trial results were applied using a single transition probability based on an exponential function, rather than applying the Kaplan-Meier data and extrapolated using a parametric function. Of note, in the previous PBAC submissions for mBC, a gamma function was fitted to both EMILIA and CLEOPATRA trials. Using different parametric functions (except Weibull function) had limited impact on the ICERs for both drugs. Using an exponential function simplifies the model, especially for the mBC setting. However, exponential parametric function may not be the best fit for the Kaplan-Meier curve and may lead to biased results. The direction of bias is unknown.
- 6.48 While there is a biological and preclinical rationale, the PBAC considered it was uncertain whether it was reasonable to assume that pertuzumab for mBC will remain as effective following prior use in eBC as there are no clinical studies to support this assumption.
- 6.49 On 1 June 2018, trastuzumab underwent a 10% statutory price reduction (SPR). The pre-PBAC response increased the rebate to ██████% (from ██████%) to take into account the 10% SPR on trastuzumab. The economic model did not include the price reduction on affected subsequent therapies. This is presented in Table 14. The PBAC noted that the ICERs in Step 7-9 of the model.

Table 14: Results of the stepped economic evaluation using pre-PBAC response updated rebate

Step and component	Base case ICER (submission prices in submission model)	Pre-PBAC response prices in submission model ICER (SPR price was not included in subsequent therapy trastuzumab arm)	Pre-PBAC price in submission model ICER (SPR price included in subsequent therapy trastuzumab arm)
Step 7 - Base case	██████	██████	██████
Step 8 - price discount of ██████% was applied to ██████ in the Ptz+T+Chemo arm	██████	██████	██████
Step 9 - price discount of ██████% (original sub) or ██████% (pre-PBAC response) was applied to the ██████ in the Ptz+T+Chemo arm	Dominant	Dominant	Dominant

ICER= Incremental cost-effectiveness ratio; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; SPR= Statutory price reduction

The redacted table shows ICERs in the range of dominant to \$105,000/QALY.

Drug cost/patient/course

6.50 The drug cost per patient per course was estimated to be \$57,727. This was based on an AEMP per vial of \$3,072.37, assuming 30% of patients are public and 70% are private patients, and one loading dose (two vials) and 16 continuing doses are received.

Estimated PBS usage & financial implications

6.51 This submission was considered by DUSC. The submission took an epidemiological approach to estimate the number of patients with HER2+, lymph node positive, eBC, based on published sources, clinician surveys and expert opinion.

6.52 Table below presents the estimated use and financial implications.

Table 15: Estimated use and financial implications

	2019	2020	2021	2022	2023	2024
Estimated extent of use						
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed, pertuzumab ^a	█	█	█	█	█	█
Estimated financial implications of pertuzumab + trastuzumab, effective prices (█% discount on █)						
Cost to PBS/RPBS	█	█	█	█	█	█
Copayments	█	█	█	█	█	█
Cost to PBS/RPBS less copayments	█	█	█	█	█	█
Estimated financial implications for trastuzumab (displaced)						
Cost to PBS/RPBS	█	█	█	█	█	█
Copayments	█	█	█	█	█	█
Cost to PBS/RPBS less copayments	█	█	█	█	█	█
Net financial implications, effective prices (█% discount on trastuzumab)						
Net cost to PBS/RPBS	█	█	█	█	█	█
Net cost to PBS/RPBS, market share approach	█	█	█	█	█	█

^a Assuming 17 per year as estimated by the submission.

^b includes a one off maximum cost for █ grandfathered Ptz+T+Chemo patients of \$█
 Source: Table 4.2.4, p129 of the submission and Sheets 2a, 2b and 3a of Utilisation and cost model.xlsx and calculated during evaluation (involving projecting the total number of trastuzumab scripts for eBC by the growth in breast cancer incidence, adjusting for patients who are lymph node positive (█%) and assuming 100% of patients currently receiving trastuzumab would receive pertuzumab)

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million per year.

6.53 The net cost to Government was \$20 – \$30 million over six years, based on the pricing discount of █% to █ to achieve budget neutrality. The net financial implications is likely to be overestimated as the estimates of the proportion of patients with eBC included locally advanced breast cancer, who are not included in the PBS restriction. The evaluation stated it was unclear why the uptake rate (█%)

would be lower than that for trastuzumab (92.3% at the end of the first year of listing)¹¹. Finally, the estimate does not take into account reduced use of pertuzumab and trastuzumab for mBC. The DUSC considered the uptake of pertuzumab in the eligible population is uncertain and that uptake could potentially be higher than █% for the population at high risk of recurrence. The DUSC noted that the benefit: harm profile will be a factor influencing use. The pre-PBAC response considered that █% was the most appropriate and justifiable uptake rate as some clinicians may treat more conservatively and not add pertuzumab to T+Chemo and changes in prescribing behaviour take time.

- 6.54 The submission argued that the net cost is due to the differing methodology for calculating new and displaced volumes. This is despite the discount on █, which aimed to achieve cost neutrality. DUSC did not accept the rationale that that the approach taken was necessary to demonstrate cost-neutrality of the listing.
- 6.55 A market share approach could have been applied based on the use of trastuzumab for eBC due to the similarity in the PBS restrictions. A market share approach conducted by the evaluation (involving projecting the total number of trastuzumab scripts for eBC by the growth in breast cancer incidence, adjusting for patients who are lymph node positive (█%) and assuming 100% of patients currently receiving trastuzumab would receive pertuzumab) resulted in slightly fewer total scripts and a net cost to Government of less than \$10 million over six years. This approach is also likely to be an overestimate as it does not take into account reduced use of pertuzumab and trastuzumab for mBC.
- 6.56 In response to evaluator’s discussion about a market share approach, the sponsor’s PSCR contained a market share analysis. This analysis used prescription counts from DHS PBS statistics website (http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp). The results are show in below.

¹¹ PBAC (October 2006) Public Summary Document – Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin®, Roche Products Pty Ltd

Table 16: PSCR revised estimates based on a market share analysis

Effective Price	2019	2020	2021	2022	2023	2024
Number of scripts dispensed, pertuzumab	████	████	████	████	████	████
Total cost to Government for PBS/RPBS	████████	████████	████████	████████	████████	████████
Total cost to Government for PBS/RPBS displaced medicines	████████	████████	████████	████████	████████	████████
Net Cost to Government for PBS/RPBS (patient co-payments removed)	████████	████████	████████	████████	████████	████████
Overall net cost to Government Health Budget of listing pertuzumab at effective price	████████	████████	████████	████████	████████	████████
Plus one off maximum cost for █████ grandfathered pertuzumab patients █████	████████					

^b includes a one off maximum cost for █████ grandfathered Ptz+T+Chemo patients of \$ █████

The redacted table shows that at year 6, the estimated number of scripts was less than 10,000 – 50,000 and the net cost to the PBS would be less than \$10 million.

6.57 This analysis did not estimate patient numbers. The total net cost is less than \$10 million over six years. This is similar to the evaluator’s market share analysis (see last row of Table 15) which estimated a total net cost of less than \$10 million over six years. The prescriptions in Table 16 are █████% and █████% lower than the submission original estimates for 2019 and 2024 respectively in Table 15.

6.58 DUSC considered that the submission had not justified the use of an epidemiological approach. DUSC considered i) the best available data to inform the utilisation of pertuzumab are PBS data for trastuzumab in the eBC setting; and ii) that a market share approach is the most appropriate method to derive the number of patients to be treated and the PBS cost-offsets associated with the listing of pertuzumab for eBC.

6.59 DUSC noted that the sponsor had appropriately provided a market share analysis in the PSCR. However the market share analysis was based only on prescription volume and DUSC considered that the estimates of usage should have had regard to the patient numbers. DUSC developed the following estimates (Table 17) of the number of treated patients. DUSC and the PBAC agreed with the submission that █████% (Advisory Board (2017 and IPSOS (2017)) was probably the best estimate of the proportion of patients with lymph node involvement. The submission estimated an uptake rate of █████% of eligible patients, however DUSC estimated this to be 90% based on Chan¹² and Harris¹³. DUSC noted that the

¹² Chan, A., and S. R. McGregor. 2012. Prevalence and management of HER2/neu-positive early breast cancer in a single institution following availability of adjuvant trastuzumab. Internal Medicine Journal 42 (3): 267-274

epidemiological approach in the submission resulted in an estimated number of patients that is not dissimilar to that based on an alternative DUSC market share approach

Table 17 DUSC estimates of patients initiating treatment with pertuzumab + trastuzumab + chemotherapy

	2019	2020	2021	2022	2023	2024
Number of patients initiating eBC treatment on trastuzumab (linear extrapolation)	■	■	■	■	■	■
% lymph node involvement	■%	■%	■%	■%	■%	■%
Number of patients initiating eBC treatment on trastuzumab with lymph node involvement	■	■	■	■	■	■
% uptake of adding pertuzumab	90%	90%	90%	90%	90%	90%
Number of initiating pertuzumab + trastuzumab	■	■	■	■	■	■

6.60 The result was an estimate of less than 10,000 initiating patients (not including grandfathered patients) in Year 1 rising to less than 10,000 in Year 6. This was ■% more than the less than 10,000 estimated by the submission in Year 1 and ■% more than the less than 10,000 estimated in Year 6. The pre-PBAC response acknowledged that a market share approach (based on existing trastuzumab PBS expenditure) provides the most accurate methodology to demonstrate budget neutrality.

6.61 As discussed in Section 2, DUSC considered that there may be use outside of the proposed restriction in patients without lymph node involvement and people already on trastuzumab + chemotherapy, who will add pertuzumab. The current wording of the restriction appears to allow this, but the submission assumes this will not occur. These patients are not included in submission estimates.

6.62 Notwithstanding the concerns about some assumptions, DUSC considers the utilisation estimates for pertuzumab presented in the submission to be reasonable overall. The PBAC noted that the financial impact of using the DUSC utilisation estimates and the pre-PBAC's pricing proposal had not been calculated. Both the DUSC revised and submission estimates do not have regard to the reduced use of pertuzumab and trastuzumab for mBC if treatment is available for eBC. Therefore the cost to the PBS was not known.

Quality Use of Medicines

6.63 No planned quality use of medicine program was noted in the submission to support the listing of Ptz+T+Chemo. The submission stated that it will undertake standard medical affairs activities, such as supporting breast cancer conferences, organising pertuzumab and eBC education meetings and providing online materials.

¹³ Harris C et al. HER2 positive early breast cancer: An Australian patterns of care study. *Pharmacoepidemiology and Drug Safety* 2014; 23(S1): 468

- 6.64 The submission noted that there are no post-marketing surveillance studies being conducted involving pertuzumab for the adjuvant treatment of eBC. Appropriate steps should be taken to understand the use of pertuzumab and the risk of AEs in the wider population. However, the submission noted that there are several other ongoing trials involving pertuzumab for eBC. The APHINITY trial also plans to follow-up patients for 10 years.

Financial Management

Risk Share Arrangement/ Rebate Arrangement/Special Pricing Arrangement

- 6.65 The submission proposed a discount for [REDACTED] to achieve a dominate ICER and a PBS/RPBS budget neutrality. The ESC noted that estimates in the submission and updated in the PSCR had a positive cost to Government, albeit much smaller than if the discount was not applied. The DUSC was concerned about the complexity of the pricing mechanism proposed to achieve cost neutrality of this listing.
- 6.66 Since submission was lodged, trastuzumab met the criteria for a 10% statutory price reduction on 1 June 2018 under sections 99ACF and 99ACL(1) of Division 3A of Part VII of the *National Health Act 1953* (Ten Year Anniversary Price Reductions). The submission did not include this reduction in the model or financial estimates, therefore the model results as well as financial estimates have been calculated using the price of trastuzumab prior to 1 June 2018.
- 6.67 It is likely that the price of trastuzumab will reduce further in the near future following registration of biosimilar medicines. The PSCR confirmed that the proposal proffered guarantees earlier savings would be generated and therefore allows for greater savings [REDACTED] overall. However, the DUSC and the ESC were uncertain whether the cost savings would be realised given the magnitude in savings that would be likely to occur when biosimilars entered the market.
- 6.68 In order to practically implement the proposed price discount ([REDACTED]%) to achieve budget neutrality, a price discount of [REDACTED]% was proposed to be applied [REDACTED] with a special pricing agreement, as the proposed effective price cannot be made public. The discount was estimated as a weighted average between a [REDACTED]% price discount for lymph node positive patients and 0% price discount for lymph node negative patients. The proportion of patients who are lymph node positive ([REDACTED]%) was based on IPSOS data and is uncertain. The proposed PBS item numbers to which [REDACTED]. The PSCR clarified that it was assumed that patients receiving 3-weekly pertuzumab would only receive 3-weekly trastuzumab and therefore PBS/RPBS item numbers for the weekly administration of trastuzumab were not included in the financial estimates. Patients would only receive weekly trastuzumab if they are unable to

tolerate 3-weekly trastuzumab. Most recent IPSOS (2018) data on the utilisation of trastuzumab shows weekly administration represents only █% of all trastuzumab eBC use (PSCR). The pre-PBAC response presented a revised discount of █% across all trastuzumab in eBC, which takes into account the 10% statutory price reduction on trastuzumab which occurred on 1 June 2018.

- 6.69 Trastuzumab is currently subsidised for a number of different indications (e.g. metastatic breast cancer, locally advanced HER2 positive breast cancer and metastatic adenocarcinoma of the stomach or gastro-oesophageal junction and breast), this would require agreement on a weighted trastuzumab price based upon the expected future utilisation across the different indications. The pre-PBAC response stated ‘the proportion of use for trastuzumab across different indications is unlikely to change with the PBS availability of pertuzumab (added to T+Chemo). A weighted price based on today’s proportion of use would be appropriate’.
- 6.70 The ESC noted that for budget neutrality to be achieved, the net cost to Government of this listing has to be nil, █. Thus the price reduction to █ that is agreed as part of this listing must be sufficient to fully offset expenditure on pertuzumab and any related costs to Government (PBS, MBS, DHS etc).

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the Section 100 (Efficient Funding of Chemotherapy), Authority Required listing of pertuzumab in combination with trastuzumab for the adjuvant treatment of patients with human epidermal growth factor 2 (HER2) positive early breast cancer (eBC) at high risk of disease recurrence. The PBAC was concerned that the modest benefit of adding pertuzumab to trastuzumab and chemotherapy was outweighed by the increased risk of AEs (in particular the cardiac risks and significant difference in experiencing diarrhoea), the uncertain magnitude of benefit in the HR+ lymph node positive patients and the uncertain place in therapy. The PBAC noted that, as the sponsor of both pertuzumab and trastuzumab, a price reduction in the █, was offered. The submission claimed that this would result in a cost-effective and budget neutral listing of pertuzumab (in combination with trastuzumab). However, the PBAC and its sub-committees were concerned that the cost-effectiveness of pertuzumab may not be maintained and the low net cost to Government may not be realised over time. However, the PBAC’s concerns regarding the sponsor’s price proposal were secondary to its concerns about the extent of clinical benefit of treatment with pertuzumab in combination with trastuzumab.
- 7.2 The PBAC noted that adding pertuzumab to trastuzumab adjuvant therapy was supported by Australian and international oncology groups. The PBAC noted that emerging new treatments and changes to current therapy protocols could potentially change the management of treatment of eBC in the adjuvant setting

and impact pertuzumab's place in therapy, as well as the applicability of the APHINITY trial results to the PBS population.

- 7.3 The submission was made under TGA/PBAC Parallel Process, with a positive TGA Delegate's Overview available at the time of the Committee's consideration but the final circumstances of registration for use in the adjuvant setting was not known. The PBAC noted that the proposed TGA indication in the Delegate's overview for pertuzumab in combination with trastuzumab and chemotherapy was "the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence". The PBAC considered "high risk patients" would include patients with lymph node positive status, however further clarity regarding the definition of "high risk patients" may be required in a PBS listing. The PBAC considered it was appropriate to align the pertuzumab listing with the current trastuzumab listing; specific comments on the restriction are discussed in Section 2 Requested Listings.
- 7.4 The PBAC considered that trastuzumab plus chemotherapy (T+Chemo) as the main comparator was appropriate.
- 7.5 The PBAC noted that the submission was based on a well-designed head-to-head randomised trial (APHINITY) comparing pertuzumab in combination with trastuzumab plus chemotherapy (Ptz+T+Chemo) (anthracycline or docetaxel plus carboplatin) to T+Chemo (anthracycline or docetaxel plus carboplatin). The submission presented a subgroup analysis by lymph node status to align the trial population with the proposed PBS listing. The safety and quality of life (QoL) data were for the intention to treat (ITT) population rather than the lymph node positive subgroup. However, the PBAC accepted the submission's argument that there was no clinically plausible reason for this subgroup of patients to have a different safety profile and QoL compared with the ITT population.
- 7.6 The PBAC noted that the reduction in the risk of recurrence (iDFS) in the lymph node positive subgroup (HR=0.77, 95% CI [0.62, 0.96]) was larger than in the ITT population ((HR=0.817, 95% CI [0.66, 1.00]), and the PBAC further noted that the difference in iDFS event-free rates increased at the 4 year time point (3.2%) compared to the 3 year time point (1.84%). Future follow up reporting dates are planned for late 2019 and 2022, with the final report expected in 2026.
- 7.7 While the PBAC agreed that it could be claimed that Ptz+T+Chemo is superior in terms of effectiveness and inferior in terms of safety compared with T+Chemo in patients with HER2 positive, lymph node positive eBC, the Committee questioned the clinical significance of the modest benefit demonstrated in the trial. In addition, the clinical benefit in patients with HR+ and lymph node positive disease was not known and the PBAC considered that this represents a large patient group who would seek PBS treatment. Overall, the PBAC was concerned that the modest benefit of adding pertuzumab to trastuzumab and chemotherapy was outweighed by the increased risk of AEs (in particular the cardiac risks and significant difference in experiencing diarrhoea), the uncertain magnitude of benefit in the HR+ lymph node positive patients and the uncertain place in therapy.

- 7.8 The submission presented a cost-utility analysis (stepped economic evaluation) which compared Ptz+T+Chemo with T+Chemo, based on the subgroup results from the APHINITY trial. The PBAC noted the submission's argument that it is irrelevant to assess the cost-effectiveness in the ITT population as reimbursement is being sought for a subgroup only. However, in agreement with ESC's view, the PBAC recalled its preference to have regard of cost-effectiveness in the ITT population in addition to the subgroup for which listing is sought.
- 7.9 The PBAC noted that importance of economic model was less determinative in this particular submission, given the price proposal and the intent of budget neutrality. While not the final price proposal, the submission applied a price discount in Step 8 of the model for an ICER/QALY which was claimed to be a cost-effective ICER of \$45,000/QALY - \$75,000/QALY (an ICER/QALY of \$45,000/QALY - \$75,000 results when the 10% statutory price reduction price of trastuzumab and subsequent therapies are incorporated). The PBAC noted this argument in the submission in light of its previous considerations, but considered that an acceptable ICER range for reimbursement of a medicine depended on the circumstances presented in an individual submission. In this case, the PBAC noted no significant differences in the overall survival were observed in the trial, but the model generated a benefit of [REDACTED] life years gained, which was nearly all derived in extrapolated portion of the model. The PBAC noted the concerns and issues raised by the ESC about the economic analysis.
- 7.10 The PBAC agreed with the DUSC's view and considered that a market share approach to be the most appropriate method for estimating the number of people that will use pertuzumab. However, the epidemiological approach in the submission resulted in an estimated number of patients that was not dissimilar to that based on an alternative DUSC market share approach. The PBAC considered that the rate of uptake in the high risk population is likely to be [REDACTED]%, although this was noted as an uncertain assumption. The PBAC noted that the financial impact based on the DUSC methodology (preferred by PBAC) and the pre-PBAC's pricing proposal had not been calculated. Thus, the overall cost to the PBS was not known.
- 7.11 The PBAC noted the special pricing arrangement proposed by the sponsor [REDACTED]. The PBAC noted that application of the discount when applied across all [REDACTED] expenditure was claimed to result in a cost of Ptz+T+Chemo that is similar to T+Chemo in the proposed listing. While the submission proposed budget neutrality (albeit there was an estimated cost to Government) over the first 6 years of listing, the PBAC and its sub-committees were concerned whether the complex pricing model would result in savings claims that would not be realised over time. Noting the established treatment benefits of T+Chemo in clinical practice, the PBAC was concerned that [REDACTED] when the additive clinical benefit of pertuzumab to the current treatment therapy was modest. This may have the impact that the claimed cost effectiveness of pertuzumab would not be maintained over time.
- 7.12 The PBAC advised that any future resubmission would need to address the

PBAC's concerns about the clinical place and the clinical benefit of pertuzumab in combination with trastuzumab, in light of the changing treatment landscape of early stage HER2+ breast cancer, and with particular focus on clinical benefit, if any, to the HR+ lymph node+ population. Future resubmission would also need to update the proposed restriction and other assumptions depending on the final product information (for example definitions of "high risk of disease recurrence"). In addition, the ESC's concerns with the economic analysis should be addressed in a resubmission. The financial implications should be recalculated following the DUSC and PBAC consideration and the proposals in the pre-PBAC response. While the PBAC welcomed the submission's intent for budget neutrality with a special pricing arrangement, the PBAC would prefer alternative arrangements that gave surety to the cost effectiveness for pertuzumab being maintained over time, given the price reductions needed to assure cost effectiveness in the current analysis [REDACTED]. In addition, a risk share agreement would also be required to mitigate higher treatment uptake than estimated and use in patients who are not at high risk of disease recurrence (such as lymph node negative disease).

7.13 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 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.