

6.04 PERTUZUMAB, Solution for I.V. infusion, 420 mg in 14 mL, Perjeta[®], Roche Products Pty Ltd.

1 Purpose of submission

1.1 The submission requested Section 100, Authority Required, Restricted Benefit listing for pertuzumab, in combination with trastuzumab and chemotherapy (T+Chemo), as neoadjuvant treatment in patients with HER2-positive locally advanced, inflammatory or early stage (≥ 2 cm in diameter or node positive) breast cancer (Table 1).

1.2 The requested listing was based on a cost-utility analysis versus T+Chemo.

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

| Component | Description |
|----------------|--|
| Population | Patients with HER2 positive, locally advanced, inflammatory or early stage (>2 cm in diameter or node positive) early breast cancer (referred to as high risk eBC). |
| Intervention | Pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of high risk eBC for up to 6 cycles. |
| Comparator | Trastuzumab in combination with chemotherapy |
| Outcomes | Primary endpoint: pathological complete response (pCR in the breast) Secondary endpoints: total pCR (in the breast and nodes), overall survival, progression-free survival, disease-free survival, adverse events |
| Clinical claim | Pertuzumab significantly improves pCR among patients with high risk early breast cancer when added to trastuzumab and chemotherapy in the neoadjuvant setting. |

Source: Table 1.1, p14 of the submission.

eBC = early breast cancer; HER2 = human epidermal growth factor receptor 2; IV = intravenous

2 Background

Registration status

2.1 Pertuzumab is TGA registered for the following indications:

Early breast cancer

Pertuzumab is indicated in combination with trastuzumab and chemotherapy for:

- the neoadjuvant treatment of patients with HER2-positive inflammatory or locally advanced, or early stage (either >2 cm in diameter or node positive) breast cancer as part of a complete treatment regimen for early breast cancer;
- the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.

Metastatic breast cancer

Pertuzumab is indicated in combination with trastuzumab and docetaxel for patients with metastatic HER2-positive breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease.

Previous PBAC consideration

- 2.2 This is the first submission for the proposed use of pertuzumab in the neoadjuvant setting.
- 2.3 Submissions for pertuzumab in the adjuvant setting were considered at the July 2018 and March 2019 PBAC meetings. Pertuzumab was not recommended due to limited clinical benefit, an uncertain ICER and unclear clinical place. The PBAC considered that the clinical place for pertuzumab in the adjuvant setting was unclear, “given the shift toward treating high-risk patients in the neoadjuvant setting and the lack of data for adjuvant pertuzumab following neoadjuvant treatment” (paragraph 7.1, pertuzumab Public Summary Document (PSD), March 2019 PBAC meeting).

3 Requested listing

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

| Name, Restriction, Manner of administration and form | Max. Amt | No. of Rpts | Dispensed Price Max Amt Public Hospital (Private Hospital) | Proprietary Name and Manufacturer |
|--|----------|-------------|---|--------------------------------------|
| PERTUZUMAB Solution for IV infusion 420 mg/14 mL, 14 mL vial | 840 mg | 0 | \$6,229.80 (\$6,355.59) | Perjeta® Roche Products Pty Ltd |

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| Category/Program: Section 100 – Efficient Funding of Chemotherapy; Public/Private Hospital |
| 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 |
| Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required - In Writing Only |
| Indication: <i>Early HER2 positive breast cancer</i> |
| Treatment Phase: Initial treatment – <i>neoadjuvant treatment</i> |
| Clinical criteria: <i>Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) either in the primary tumour or a metastatic lesion</i> AND Patient must have locally advanced, inflammatory or early stage (tumour >2 cm in diameter or lymph node positive) breast cancer AND <i>Patient must not have undergone surgery for this condition</i> AND Patient must commence treatment concurrently with trastuzumab <i>The treatment must be in combination with trastuzumab.</i> AND Patient must commence treatment concurrently with chemotherapy <i>The treatment must be in combination with chemotherapy.</i> |

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| <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>Patient must not receive more than 1 treatment cycle under this restriction.</p> |
| <p>Prescribing Instructions:</p> <p>Authority applications for initial treatment must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(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)</p> <p>(ii) a copy of the signed patient acknowledgement form.</p> <p>HER2 positivity must be demonstrated by in situ hybridisation (ISH).</p> <p>Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval.</p> <p>Treatment with this drug for this condition must not exceed 6 treatment cycles (18 weeks) of combined initial and continuing treatment</p> |
| <p>Administrative Advice:</p> <p>Authority applications for initial treatment must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(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</p> <p>(ii) a copy of the signed patient acknowledgement form.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> |
| <p>Administrative Advice:</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> |

| Name, Restriction, Manner of administration and form | Max. Amt | No. of Rpts | Dispensed Price | | Proprietary Name and Manufacturer |
|--|----------|-------------|----------------------------|--------------------|-----------------------------------|
| | | | Max Amt Public Hospital | (Private Hospital) | |
| PERTUZUMAB Solution for IV infusion 420 mg/14 mL, 14 mL vial | 420 mg | 4 | \$3,157.43 (\$3,240.20) | | Perjeta® Roche Products Pty Ltd |
| Category/Program: Section 100 – Efficient Funding of Chemotherapy; Public/Private Hospital | | | | | |
| 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 | | | | | |
| Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic | | | | | |

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|---|
| Episodicity: Neoadjuvant treatment |
| Condition: HER2 positive early breast cancer |
| Indication: <i>Early HER2 positive breast cancer</i> |
| Treatment Phase: Continuing treatment – <i>neoadjuvant treatment</i> |
| <p>Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND <i>Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.</i> AND Patient must commence treatment concurrently with trastuzumab The treatment must be in combination with trastuzumab. AND Patient must commence treatment concurrently with chemotherapy The treatment must be in combination with chemotherapy. 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 <i>Patient must not receive more than 5 treatment cycles under this restriction</i></p> |
| <p>Prescribing Instructions: Increased maximum quantity will be authorised where a patient requires a new loading dose due to a break in therapy of more than 1 week but less than 6 weeks from the last dose. <i>Treatment with this drug for this condition must not exceed 6 treatment cycles (18 weeks) of combined initial and continuing treatment</i></p> |
| <p>Administrative Advice: Authority applications for increased quantities/repeats (where relevant) may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday) <i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised.</i></p> |

- 3.2 The submission did not propose a special pricing arrangement.
- 3.3 The proposed price for pertuzumab in the neoadjuvant setting is the same as the current price for pertuzumab in the metastatic setting (AEMP = \$3,072.37 per 420 mg vial).
- 3.4 There were inconsistencies between the proposed restrictions and the clinical evidence presented, including:
- Only treatment naïve patients were included in the clinical trials. While implied in the restrictions, the ESC considered this should be made clear in the restrictions.
 - The proposed threshold for left ventricular ejection fraction (LVEF) is $\geq 45\%$ before initiating treatment with pertuzumab. The included trials recruited patients with LVEF $\geq 55\%$ at baseline. The proposed threshold of $\geq 45\%$ is also inconsistent with the TGA Product Information which recommends a pre-treatment LVEF of $\geq 55\%$ in patients with early breast cancer. During the previous consideration of

pertuzumab for adjuvant treatment, the ESC noted that the change in LVEF is the clinically important measure, rather than the absolute value. Further, it was considered unlikely that clinicians would treat patients with serious cardiac disease/illness with pertuzumab, noting that these patients were excluded from the APHINITY trial. The ESC previously considered that on balance, it would be appropriate to align the LVEF criteria with the current trastuzumab listing (LVEF $\geq 45\%$) to allow patients to be eligible for both drugs if they are to be used concurrently (paragraph 2.3, pertuzumab, Public Summary Document, March 2019 PBAC meeting). The Pre-Sub-Committee Response (PSCR) noted, and agreed with, these comments.

- The restriction is based on six cycles of pertuzumab, whereas the trials that measured comparative effectiveness, NEOSPHERE and PEONY, used only four cycles.
- The restriction did not specify the chemotherapy agent or regimen to be used in combination with Ptz+T. Docetaxel (D) was used in both the NEOSPHERE and PEONY trials. The benefits and/or harms of Ptz+T+Chemo may differ from those of Ptz+T+D. The PSCR argued that taxanes are the most commonly used neoadjuvant chemotherapy backbone, and in Australia paclitaxel is considered the taxane of choice to avoid diarrhoea (IPSOS 2018). The ESC and DUSC considered it was reasonable to not specify the chemotherapy regimen in the restriction.
- The requested listing for patients with inflammatory breast cancer was based on comparative effectiveness data from only 17 patients in NEOSPHERE (patients with inflammatory breast cancer were excluded from PEONY). The PSCR noted inflammatory breast cancer is expected to account for 1-2% of new BC cases in Australia and has a disproportionately higher death rate than other BC types. In NEOSPHERE, patients with inflammatory breast cancer comprised 17/214 (7.9%) of the combined Ptz+T+Chemo and T+Chemo arms and were therefore overrepresented in the trial. The PSCR argued that, although the patient sample size is small, the evidence for Ptz+T+Chemo in inflammatory BC in NEOSPHERE is a good representation of outcomes in this patient cohort.

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

4 Population and disease

- 4.1 Breast cancer was the most common cancer diagnosis for women in Australia in 2018. It was estimated that 19,371 females and 164 males¹ would be newly diagnosed with breast cancer in 2019 in Australia, representing 14% of all new cancer diagnoses in the year. The estimated number of deaths from breast cancer was estimated to be 3,058

¹ Males represent 0.84% of all the newly diagnosed breast cancer in Australia in 2019.

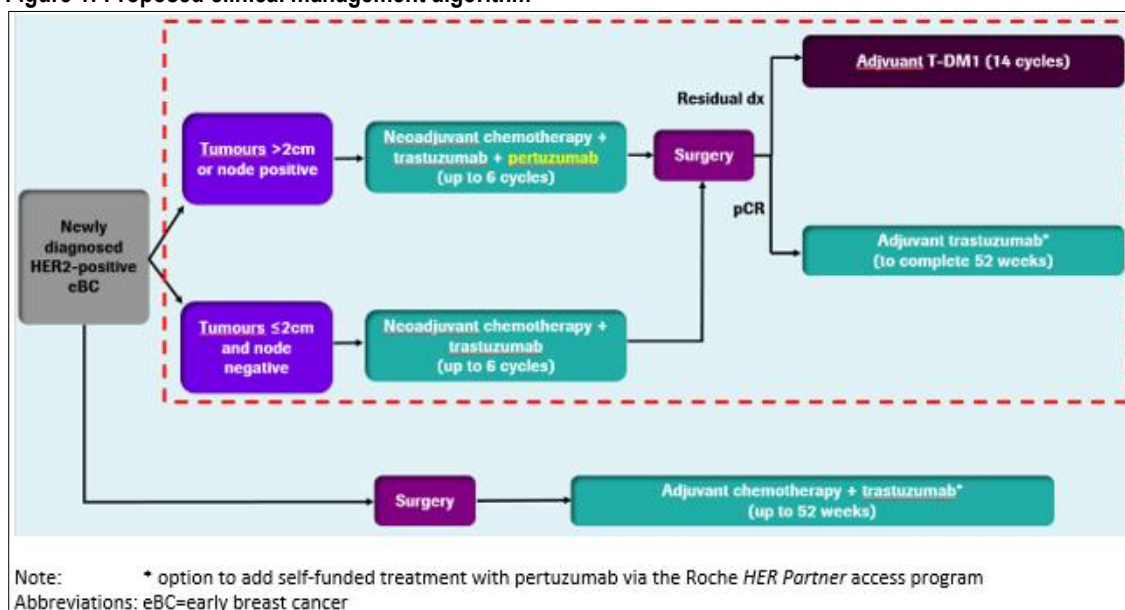
females and 32 males² in 2019, contributing to 6.2% of all cancer deaths.³ The submission reported that about 94% of breast cancer patients are diagnosed with early breast cancer and 15% of the patients are HER2-positive.

- 4.2 Pertuzumab is a recombinant humanised monoclonal antibody which targets a subdomain of the HER2 receptor.
- 4.3 The submission proposed the addition of pertuzumab to T+Chemo as neoadjuvant treatment in patients with HER2-positive, locally advanced, inflammatory or early stage (tumour >2 cm in diameter or lymph node positive) breast cancer (referred to in the submission as high risk early breast cancer) (Figure 1). The proposed clinical management algorithm included two adjuvant treatment arms: (a) trastuzumab treatment for patients who achieve pathological complete response (pCR), or (b) trastuzumab emtansine (T-DM1) for patients who have residual disease. T-DM1 was recommended by the PBAC at the November 2019 meeting and listed on the PBS from 1 April 2020 for the adjuvant treatment of patients with HER2-positive early breast cancer with residual disease following neoadjuvant treatment with HER2-targeted therapy.
- 4.4 Anthracyclines are a key component of neoadjuvant chemotherapy in clinical practice as they improve pCR rates. The ESC noted the addition of neoadjuvant pertuzumab may reduce the extent of use of anthracyclines in the neoadjuvant setting due to an increased risk of cardiac toxicity and may move the use of anthracyclines to the adjuvant setting (as in the NEOSPHERE and PEONY trials). The ESC noted that the impact of this change on clinical outcomes is unknown. The pre-PBAC response agreed that the use of anthracyclines sequentially prior to T+Chemo is part of standard of care and anthracyclines are most commonly used in high risk eBC patients, however the sponsor maintained that the PBS listing of pertuzumab would not impact on clinicians' use of anthracyclines in the neoadjuvant setting and hence is not anticipated to increase the use of anthracyclines in the adjuvant setting.

² Males represent 1.04% of all deaths from breast cancer in Australia in 2019.

³ *Breast cancer in Australia statistics*, Cancer Australia, accessed 17 January 2019, <https://breast-cancer.canceraustralia.gov.au/statistics>.

Figure 1: Proposed clinical management algorithm



Source: Figure 1.3, p23 of the submission

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

5 Comparator

- 5.1 The submission nominated the combination therapy of T+Chemo as the main comparator. Trastuzumab and taxane-based chemotherapy is the current standard of care in the target population according to Australian and international guidelines.
- 5.2 At the November 2019 meeting, the PBAC 'noted that the availability of T-DM1 in the adjuvant setting would change the treatment algorithm and improve patient outcomes. The PBAC considered that any future submissions for therapies for HER2+ eBC would need to account for the availability and efficacy of T-DM1 and demonstrate benefit in a treatment algorithm that includes T-DM1' (para 7.3, trastuzumab emtansine, Public Summary Document, November 2019). Thus the ESC considered the relevant comparison was sequential pertuzumab and T-DM1 (Ptz+T+Chemo followed by T-DM1 in the adjuvant setting for patients without a pCR) compared with T-DM1 (T+Chemo followed by T-DM1 in the adjuvant setting for patients without a pCR). The PSCR argued that adjuvant T-DM1 is intended for use in only a small proportion of patients with a specific type of early breast cancer. The ESC noted that the population eligible for T-DM1 may be up to half the patients eligible for pertuzumab based on pCR rates in NEOSPHERE. The ESC noted that the KATHERINE T-DM1 trial included some patients (18%) who were treated with neoadjuvant pertuzumab and considered this trial could provide context regarding sequential use of pertuzumab and T-DM1.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (7) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with neoadjuvant pertuzumab, noting potential improvements in pCR and associated tumour shrinkage and better surgical options for patients, as well as improvements in prognosis and quality of life. The comments noted that pertuzumab is currently well tolerated and the toxicities are manageable.
- 6.3 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) that extending the availability of pertuzumab to the neoadjuvant setting was supported by the NEOSPHERE trial. The BCNA noted that T-DM1 in the adjuvant setting was recently recommended by the PBAC and that pertuzumab in the neoadjuvant setting would be welcomed by the community as it would provide another option for early breast cancer patients.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the pertuzumab submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of increased pCR in the NEOSPHERE trial, while noting that it was demonstrated that pertuzumab had unknown overall survival (OS) benefit, and no progression free survival (PFS) or quality of life benefit. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for Ptz+T+Chemo, which was limited to C (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)⁴, based on a comparison with T+Chemo.

Clinical trials

- 6.5 The submission based comparative efficacy on one Phase II, open label, randomised four-arm trial, NEOSPHERE, comparing four cycles of Ptz+T+D (N=107) versus four cycles of T+D (N=107) in the neoadjuvant setting, in treatment-naïve women with HER2-positive breast cancer.
- 6.6 The submission identified a second phase II, open label, randomised three-arm trial, TRYPHAENA, which compared six cycles of pertuzumab, trastuzumab and either anthracycline-based (N=73) or carboplatin-based (N=77) chemotherapy, as

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

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neoadjuvant treatment, in women with early and advanced HER2 breast cancer. Results were used as supportive evidence for tolerability and safety.

- 6.7 PEONY is a Phase III, double-blind, randomised trial comparing four cycles of Ptz+T+D (N=219) versus four cycles of T+D (N=110) as neoadjuvant treatment in chemotherapy-naïve Asian patients with HER2+ early or locally advanced breast cancer (Shao 2019). The submission excluded the PEONY trial on the grounds of “incorrect intervention”. As the results of total pCR after neoadjuvant treatment and surgery are relevant to the current submission the evaluators included the results from the PEONY trial in the Commentary. The PSCR claimed that despite not being formally included in the submission, the results of PEONY support the main claim of superior efficacy with the addition of pertuzumab to neoadjuvant trastuzumab and chemotherapy. The ESC considered it was appropriate for this trial to be included.
- 6.8 Details of the trials presented in the submission, together with PEONY, are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

| Trial ID | Protocol title/ Publication title | Publication citation |
|----------------------------|---|---|
| NEOSPHERE (NCT00545688) | <p>Clinical Study Report WO20697 - A randomised, multicenter, multinational Phase II study on trastuzumab plus docetaxel versus trastuzumab plus docetaxel plus pertuzumab versus trastuzumab plus pertuzumab versus pertuzumab and docetaxel in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer.</p> <p>Primary CSR WO20697 (Report No. 1032196), version 3, June 2011 Update CSR WO20697 (Report No. 1053542), March 2013. Second Update CSR WO20697 (Report No. 1057938), February 2014. Final CSR WO20697 (Report No. 1062345), February 2015.</p> <p>Gianni L, Pienkowski T, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial.</p> <p>Gianni L, De La Haba-Rodriguez J, et al. Cardiac safety of pertuzumab-and trastuzumab-based therapy: Neosphere and tryphaena joint analysis [Conference Abstract]</p> <p>Gianni L, Pienkowski T, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial.</p> | <p><i>Lancet</i> 2012; 13(1):25-32</p> <p><i>Breast</i> 2013; 22(S1): S102</p> <p><i>Lancet</i> 2016; 17(6):791-800</p> |
| TRYPHAENA (NCT00976989) | <p>Clinical Study Report BO22280 - A randomised, multicentre, multinational Phase II study to evaluate pertuzumab in combination with trastuzumab, given either concomitantly or sequentially with standard anthracycline-based chemotherapy or concomitantly with a non-anthracycline-based chemotherapy regimen, as neoadjuvant therapy for patients with locally advanced, inflammatory or early stage HER2-positive breast cancer.</p> <p>Primary CSR BO22280 (Report No. 1046609), May 2012. Update CSR BO22280 (Report No. 1052838), December 2012. Second Update CSR BO22280 (Report No. 1058102), January 2014. Final CSR BO22280 (Report No. 1069778), September 2016.</p> | |

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| Trial ID | Protocol title/ Publication title | Publication citation |
|------------------------|--|--|
| | <p>Schneeweiss A, Chia S, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA)</p> <p>Schneeweiss A, Chia S, et al. Abstract P4-21-02: Pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: Efficacy analysis of a phase II cardiac safety study (TRYPHAENA) [abstract]. In: <i>Proceedings of the 2016 San Antonio Breast Cancer Symposium</i>; 2016 Dec 6-10; San Antonio, TX. Philadelphia (PA): American Association for Cancer Research.</p> <p>Schneeweiss A, Chia S, et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer.</p> | <p><i>Annals of Oncology</i> 2013; 24(9): 2278-2284.</p> <p><i>Cancer Research</i> 2017; 77(4 Suppl): Abstract nr P4-21-02.</p> <p><i>European Journal of Cancer</i> 2018; 89:27-35.</p> |
| PEONY (NCT02586025) | <p>Protocol title: A randomised, multicentre, double-blind, placebo-controlled, Phase III study to evaluate pertuzumab in combination with docetaxel and trastuzumab as adjuvant therapy, and pertuzumab in combination with trastuzumab as adjuvant therapy after surgery and chemotherapy in patients with early-stage or locally advanced HER2-positive breast cancer, December 2016.</p> <p>Shao Z, Pang D, et al. Efficacy, Safety, and tolerability of pertuzumab, trastuzumab, and docetaxel for patients with early or locally advanced ERBB2-positive breast cancer in Asia - the PEONY phase 3 randomized clinical trial.</p> | <p>JAMA Oncology Published online October 24, 2019. doi:https://doi.org/10.1001/jamaoncol.2019.3692</p> |

Source: Table 2.4, p37 of the submission.

CSR = Clinical Study Report; HER2 = human epidermal growth factor receptor 2

6.9 The key features of the randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

| Trial | N | Design/ duration [^] | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
|---|-------------------|---|-----------------|--|--|-------------------------------------|
| Neoadjuvant setting: Ptz+T+D vs. T+D | | | | | | |
| Adjuvant setting: FEC+T (3 cycles) followed by T (10 cycles) | | | | | | |
| NEOSPHERE | 107 vs. 107 | Randomised, open label, Phase II; 4 cycles (q3w) | Moderate | HER2-positive operable (T2–3, N0–1, M0), locally advanced (T2– 3, N2–3, M0 or T4a–c, any N, M0), or inflammatory (T4d, any N, M0) BC; primary tumour >2 cm chemotherapy-naïve | Primary: bpCR ⁻ tpCR ⁻ (post-hoc) Secondary: PFS | Not used Not used Yes |
| PEONY | 219 vs. 110 | Randomised, double-blind, placebo- controlled, Phase III; 4 cycles (q3w) | Low | HER2-positive; early-stage (T2-3, N0-1, M0) or locally advanced (T2-3, N2 or N3, M0; T4, any N, M0) BC; primary tumour >2 cm; chemotherapy-naïve; Asia-Pacific | Primary: tpCR [#] | Not used |
| Neoadjuvant setting: Ptz+T+ FEC,D vs. Ptz+T+carboplatin,D | | | | | | |
| Adjuvant setting: T (11 cycles) | | | | | | |
| TRYPHAENA | 73 vs. 77 | Randomised, open label, Phase II; 6 cycles (q3w) | Moderate | HER2-positive operable (T2-3, N0-1, M0), locally advanced (T2- 3, N2 or N3, M0; T4a-c, any N, M0) and inflammatory (T4d, any N, M0) | Primary: bpCR ⁻ | Not used |

Source: Table 1, Attachment 2 of the submission; Schneeweiss (2013); Shao (2019); pp48-49 in Protocol for PEONY (YO28762), version 4, December 2016 (available at: <https://clinicaltrials.gov/ct2/show/NCT02586025>; accessed 16 December 2016).

BC = breast cancer; bpCR = pCR in the breast; D = docetaxel; DFS = disease-free survival; EFS = event-free survival; N = number randomised; OL = open label; OS = overall survival; pCR = pathological complete response; PFS = progression-free survival; Ptz = pertuzumab; q3w = once every 3 weeks; T = trastuzumab; tpCR = total pCR; vs = versus.

[^] Duration of neoadjuvant treatment

In NEOSPHERE, adjuvant treatment: both Arm Ptz+T+D and Arm T+D: FEC x3 cycles (cycle 5-7); and T x13 cycles (cycle 5-17); post-treatment follow-up = 5 years post-randomisation.

In PEONY, adjuvant treatment: Arm Ptz+T+D: FEC x3 cycles (cycle 5-7); and Ptz+T x13 (cycle 8-20); Arm Placebo+T+D: FEC x3 cycles (cycle 5-7); and Placebo+T x13 (cycle 8-20); post-treatment follow-up up to one year in total.

⁻ Assessed by local pathologist, no independent review.

[#] Assessed by an Independent Review Committee (IRC).

In NEOSPHERE, adjuvant FEC = 5-fluorouracil 600 mg/m², epirubicin 90 mg/m² and cyclophosphamide 600 mg/m².

In TRYPHAENA (Arm A), neoadjuvant FEC = 5-fluorouracil 500 mg/m², epirubicin 100 mg/m² and cyclophosphamide 600 mg/m².

In PEONY, adjuvant FEC = 500–600 mg/m² 5-fluorouracil (5-FU), 90–120 mg/m² epirubicin, and 500–600 mg/m² cyclophosphamide.

6.10 Both NEOSPHERE and TRYPHAENA were open label trials with treatment allocation not concealed from the patients, investigators or outcome assessors. Assessors of clinical tumour response were not blinded. Pathological tumour response was assessed by a local pathologist who was considered unlikely to know the treatment allocation. There was no central/independent review of the accuracy of the pathology results. Risk of bias is therefore considered moderate in both NEOSPHERE and TRYPHAENA. PEONY was a double-blind trial and the primary outcome of total

pathological complete response (tpCR) was determined by an Independent Review Committee (IRC)⁵. Risk of bias in PEONY is therefore considered low.

- 6.11 The proposed PBS population includes females and males, and according to Cancer Australia statistics approximately 1% of breast cancer patients are male (para. 4.1).⁶ However, NEOSPHERE and TRYPHAENA excluded males and while PEONY did not exclude males, 100% of the trial participants were female.
- 6.12 The ESC and DUSC noted that in clinical practice anthracyclines are frequently used in the neoadjuvant setting as they improve pCR rates. However, neoadjuvant anthracycline was omitted from the trial protocols for NEOSPHERE and PEONY, where anthracyclines were given following surgery. Thus, the ESC and DUSC considered that it was uncertain whether the results from the trials would be reflective of clinical outcomes in practice. The PBAC agreed and considered this to be a key concern in terms of applicability of the evidence to clinical practice.
- 6.13 The proposed PBS listing is for pertuzumab in combination with T+Chemo. Docetaxel was the chemotherapy agent used in both the NEOSPHERE and PEONY trials. The applicability of the trial results to the PBS population when other chemotherapy agents are used is therefore uncertain. The PSCR argued that efficacy has been demonstrated with a range of chemotherapy regimens in combination with trastuzumab and pertuzumab. The ESC considered that not all chemotherapy regimens would be expected to be equally effective.

Comparative effectiveness

- 6.14 Table 4 presents a summary of the pCR and clinical tumour response outcomes across the three trials. Table 5 presents a summary of the survival outcomes: OS, PFS and disease-free survival (DFS) for NEOSPHERE and TRYPHAENA. Figure 2 presents the Kaplan-Meier estimates of PFS by treatment arm for NEOSPHERE. The only outcome included in the economic analysis was PFS from NEOSPHERE. The PBAC noted that the primary endpoint in NEOSPHERE was bpCR and tpCR was presented as an exploratory analysis only.

⁵ An IRC consisted of independent experts who were not involved in the study (including three pathologists) was used to evaluate the pathologic response. The IRC remains blinded to the treatment assignment for the formal efficacy analyses. The Sponsor remains blinded to the IRC assessments (p9, Statistical Analysis Plan YO28762, July 2017).

⁶ 0.84% of the patients newly diagnosed with breast cancer were men and 1.04% of deaths from breast cancer were men in Australia in 2019.

Table 4: Summary of efficacy outcomes in NEOSPHERE, PEONY and TRYPHAENA (Note 1)

| | Pertuzumab n/N (%) | Comparator n/N (%) | RR (95% CI) | Difference % (95% CI), p-value |
|---|-----------------------|-----------------------|--------------------------|---|
| Pathological complete response in the breast (bpCR) | | | | |
| NEOSPHERE | 49/107 (45.8) | 31/107 (29.0) | 1.58 (1.10, 2.27) | 16.8 (3.5, 30.1), p=0.0141* |
| PEONY | NR | NR | - | - |
| TRYPHAENA-Arm A | 45/73 (61.6) | - | - | - |
| TRYPHAENA-Arm C | 51/77 (66.2) | - | - | - |
| Total pathological complete response (tpCR) | | | | |
| NEOSPHERE | 42/107 (39.3) | 23/107 (21.5) | 1.83 (1.19, 2.81) | 17.8 (4.6, 31.0), p=.008[^] |
| PEONY [‡] | 86/219 (39.3) | 24/110 (21.8) | 1.80 (1.22, 2.66) | 17.5 (6.9, 28.0), p=.001 |
| TRYPHAENA-Arm A | 41/73 (56.2) | - | - | - |
| TRYPHAENA-Arm C | 49/77 (63.6) | - | - | - |
| Clinical response (best tumour response[^] = complete response or partial response) | | | | |
| NEOSPHERE | 89/101 (88.1) | 79/99 (79.8) | 1.10 (0.98, 1.25) | 8.3 (-2.4, 19.0) |
| PEONY | 194/219 (88.6) | 86/110 (78.2) | 1.13 (1.02, 1.26) | 10.4 (1.1, 19.4) |
| TRYPHAENA-Arm A | 67 (92.1) | - | - | - |
| TRYPHAENA-Arm C | 69/ (89.7) | - | - | - |
| Clinical complete response (best tumour response[^] = complete response) | | | | |
| NEOSPHERE | 31/101 (30.7) | 23/99 (23.2) | 1.32 (0.83, 2.10) | 7.5 (-5.4, 20.3) |
| PEONY | 24/219 (11.0) | 11/110 (10.0) | 1.10 (0.56, 2.15) | 1.0 (-6.5, 8.4) |
| TRYPHAENA-Arm A | 37/73 (50.7) | - | - | - |
| TRYPHAENA-Arm C | 31/77 (40.3) | - | - | - |
| Time to clinical response, primary breast lesion, weeks, median (80% CI) [min, max] | | | | |
| NEOSPHERE | 6.3 (4, 7) [3, 13] | 6.3 (6, 7) [3, 13] | - | - |
| PEONY | NR | NR | - | - |
| TRYPHAENA-Arm A | 3.6 (3, 6) [3, 18] | - | - | - |
| TRYPHAENA-Arm C | 4.9 (4, 6) [3, 18] | - | - | - |

Source: Table 2.45, pp84-85 of the submission; Shao (2019) for PEONY.

C = carboplatin; CI = confidence interval; D = docetaxel; n = number of participants with event; N = total participants in group; NR = not reported; P = pertuzumab, bpCR = pathological complete response in the breast (ypT0/is); RD = risk difference; RR = rate ratio; T = trastuzumab; tpCR = total pathological complete response (ypT0/is ypN0)

Bold indicates statistically significant results.

*p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment

[^] The submission reported that results were calculated post-hoc and not adjusted for multiplicity (p57 of the submission).

[‡] tpCR was determined by an Independent Review Committee (IRC) in PEONY.

[^] Tumour response was by clinical breast examination (CBE) in NEOSPHERE and/or mammogram in TRYPHAENA. Tumour response in PEONY was by a breast magnetic resonance imaging (MRI) and CBE at baseline, with disease status evaluated by additional conventional methods (mammogram, ultrasound, CT scans or x-rays as per local clinical practice (p13, Protocol YO28762, version 4). Best tumour response represents the best overall response during the neoadjuvant period.

Note 1: Neoadjuvant treatment evaluated:

NEOSPHERE: four cycles of Ptz+T+D versus four cycles of Ptz+D;

PEONY: four cycles of Ptz+T+D versus four cycles of Placebo+T+D; and

TRYPHAENA: three cycles of Ptz+T+FEC followed by three cycles of Ptz+T+D in Arm A, Ptz+T+C+D x6 in Arm C (FEC = 5-fluorouracil 500 mg/m², epirubicin 100 mg/m² and cyclophosphamide 600 mg/m²).

Raw data from PEONY are presented in *italics* as PEONY was not presented in the submission. Shao (2019) presented the treatment effect estimates (RR, RD) for tpCR in PEONY. All the other treatment effect estimates for PEONY were calculated using the raw data reported in Shao (2019) and using the same method as used in Shao (2019). Treatment effect estimates (RD for NEOSPHERE were calculated using the same method as in the submission.

Table 5: Overview of survival outcomes in NEOSPHERE, TRYPHAENA (Note 1)

| | Pertuzumab n/N (%) | | Nothing or Placebo n/N (%) | | RR (95% CI) |
|---|-----------------------|-------------------|-------------------------------|--------------|----------------------|
| OS (events, total treatment period), n (%) | | | | | |
| NEOSPHERE | 8 (7.5) | | 6 (5.6) | | NR |
| TRYPHAENA-Arm A | 5/73 (6.8) | | - | | - |
| TRYPHAENA-Arm C | 10/77 (13.0) | | - | | - |
| OS (1-year survival), % (95% CI) | | | | | |
| NEOSPHERE | - | | - | | - |
| TRYPHAENA-Arm A | 69 | 99 (96, 100) | - | | - |
| TRYPHAENA-Arm C | 72 | 99 (96, 100) | - | | - |
| OS (5-year survival), % (95% CI) | | | | | |
| NEOSPHERE | - | | - | | - |
| TRYPHAENA-Arm A | 45 | 93 (87, 99) | - | | - |
| TRYPHAENA-Arm C | 51 | 87 (79, 95) | - | | - |
| PFS (events), n (%) | | | | | |
| NEOSPHERE | 17/107 (15.9) | | 19/107 (17.8) | | NR |
| TRYPHAENA-Arm A | 10/73 (13.7) | | - | | - |
| TRYPHAENA-Arm C | 14/77 (18.2) | | - | | - |
| PFS (1-year survival), % (95% CI) | N* | % (95% CI) | | | |
| NEOSPHERE | 99 | 96 (92, 100) | 101 | 98 (95, 100) | NR |
| TRYPHAENA-Arm A | 67 | 96 (91, 100) | - | | - |
| TRYPHAENA-Arm C | 72 | 99 (96, 100) | - | | - |
| PFS (5-year survival), % (95% CI) | N* | % (95% CI) | | | |
| NEOSPHERE | 63 | 86 (77, 91) | 58 | 81 (71, 87) | HR=0.69 (0.34, 1.40) |
| TRYPHAENA-Arm A | 37 | 85 (77, 94) | - | | - |
| TRYPHAENA-Arm C | 42 | 81 (71, 90) | - | | - |
| DFS (events), n (%) | | | | | |
| NEOSPHERE | 15/107 (14.9) | | 18/107 (17.5) | | NR |
| TRYPHAENA-Arm A | 10/69 (14.5) | | - | | - |
| TRYPHAENA-Arm C | 11/72 (15.3) | | - | | - |
| DFS (1-year survival), % (95% CI) | N* | % (95% CI) | | | |
| NEOSPHERE | 96 | 96 (92, 100) | 92 | 95 (91, 99) | NR |
| TRYPHAENA-Arm A | 66 | 96 (91, 100) | - | | - |
| TRYPHAENA-Arm C | 67 | 96 (91, 100) | - | | - |
| DFS (3-year survival) | N* | % (95% CI) | | | |
| NEOSPHERE | 88 | 92 (87, 97) | 79 | 85 (77, 92) | |
| DFS (5-year survival) | N* | % (95% CI) | | | |
| NEOSPHERE | 17 | 84 (72, 91) | 12 | 81 (72, 88) | HR=0.60 (0.28, 1.27) |
| TRYPHAENA-Arm A | 2 | 85 (77, 94) | - | | - |
| TRYPHAENA-Arm C | 0 | Note 2 | - | | - |

Source: Table 2.17, p57 of the submission; Table 2.22, p61 of the submission; Shao (2019).

C = carboplatin, CI = confidence interval, D = docetaxel, HR = hazard ratio, n = number of participants with event, N = total participants in group, NR = not reported, Ptz = pertuzumab, RR = rate ratio, T = trastuzumab

Bold indicates statistically significant results.

* Number at risk

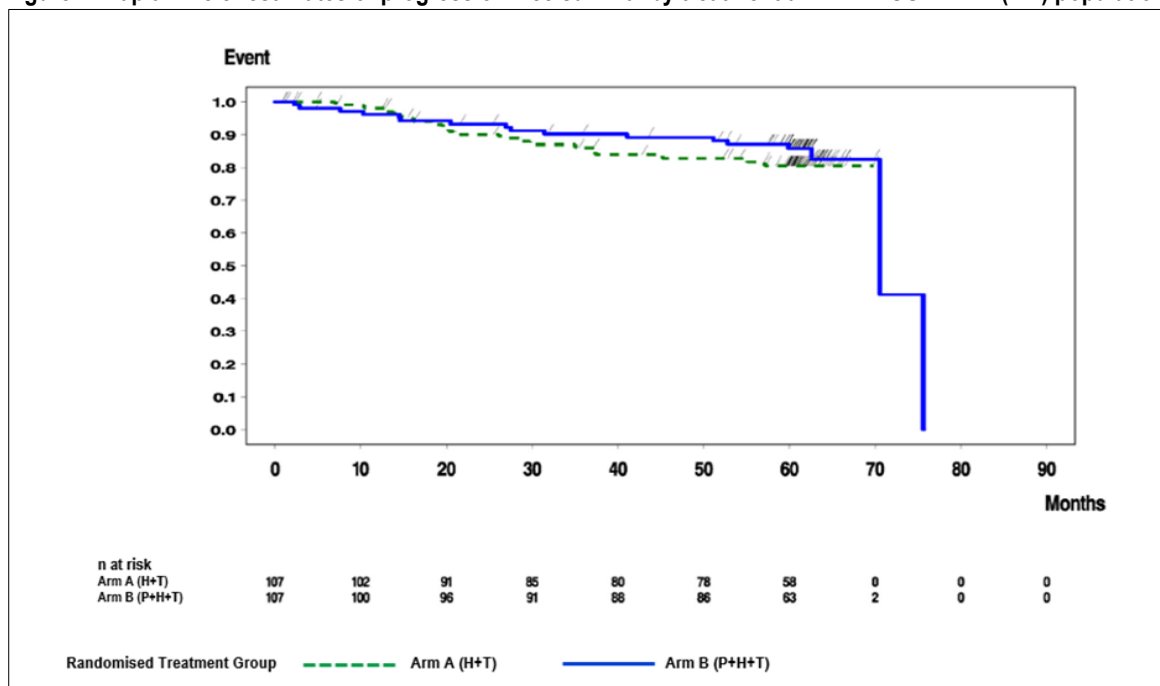
Note 1: Neoadjuvant treatment evaluated:

NEOSPHERE: Ptz+T+D x4 versus Ptz+D x4;

TRYPHAENA: Ptz+T+FEC x3 → Ptz+T+ x3 in Arm A, Ptz+T+C+D x6 in Arm C (FEC = 5-fluorouracil 500 mg/m², epirubicin 100 mg/m² and cyclophosphamide 600 mg/m²).

Note 2: the submission reported that the 5-year DFS survival rate for Arm C was not reported because most patients had not reached the time point at the end of the study (Table 2.45, pp84-85 of the submission).

Figure 2: Kaplan-Meier estimates of progression-free survival by treatment arm in NEOSPHERE (ITT) population



Source: Figure 2.4, p59 of the submission.

- 6.15 The submission claimed that the data from NEOSPHERE demonstrated that in the proposed population using four cycles of neoadjuvant Ptz+T+D resulted in superior efficacy compared to T+D on the basis that “Ptz+T+Chemo led to a statistically significant and clinically meaningful improvement in pCR, with a difference of 16.8% (95% CI 3.5%, 30.1%) exceeding the proposed Minimal Clinically Important Difference (MCID) of 15% (p=0.0141)” (p84 of the submission). The analysis of tpCR, as recommended by the FDA and the EMA, also demonstrated a statistically significant and clinically meaningful improvement in pCR, with a difference of 17.8% (95% CI 4.6%, 31.0%) (p=0.008). The ESC noted that there was limited justification provided for the MCID of 15% and considered that the improvement in pCR may not be clinically meaningful, especially with the availability of T-DM1 in the adjuvant setting for patients without a pCR.
- 6.16 The ESC noted that the bpCR rate for the pertuzumab arm in NEOSPHERE (45.8%) was similar to pCR rates in trials with anthracyclines but no pertuzumab in the neoadjuvant setting (45-55%^{7,8}). This suggests that pertuzumab may not be contributing to an increase in pCR rates above that achieved with the use of neoadjuvant anthracyclines.

⁷ Robidoux A, Tang G, Rastogi P, et al: Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): An open-label, randomised phase 3 trial. *Lancet Oncol* 14:1183-1192, 2013

⁸ Buzdar, A. et al. ACOSOG Z1041 (Alliance): Definitive analysis of randomized neoadjuvant trial comparing FEC followed by paclitaxel plus trastuzumab (FEC → P+T) with paclitaxel plus trastuzumab followed by FEC plus trastuzumab (P+T → FEC+T) in HER2+ operable breast cancer. *Journal of Clinical Oncology* 2013 31:15_suppl, 502-502

- 6.17 The submission also reported that the PFS and DFS results from NEOSPHERE were supportive of the benefit of Ptz+T+D and an association between the clinically significant improvement in pCR and better long-term efficacy outcomes. In addition, the submission noted an improved PFS and DFS after 5-year follow-up suggested a “persistent therapeutic effect” of the neoadjuvant treatment with Ptz+T+D (p84 of the submission). This claim is not supported by the evidence presented. The PFS and DFS were not statistically significant with hazard ratios of 0.69 (95% CI 0.34, 1.40) and 0.60 (95% CI 0.28, 1.27) respectively.
- 6.18 TRYPHAENA compared six cycles of Ptz+T with anthracycline-based versus carboplatin-based neoadjuvant chemotherapy regimens. The submission reported that the results of pCR (bpCR, tpCR) and longer-term survival outcomes (OS, PFS and DFS) supported the results observed in NEOSPHERE. However, the use of survival outcomes in TRYPHAENA is limited because there was no comparative evidence of effectiveness of Ptz+T+Chemo vs. T+Chemo. The higher rates of bpCR and tpCR observed in TRYPHAENA compared with NEOSPHERE could be attributed to the use of six cycles of HER2 therapy, compared to four cycles in NEOSPHERE, as suggested in the submission (p65). The TGA considered the higher pCR rate in TRYPHAENA is likely to be a result of combining polychemotherapy with the anti-HER2 therapies in the neoadjuvant setting.⁹ The ESC agreed with the TGA comment and considered that the higher rates of pCR in TRYPHAENA compared with NEOSPHERE may have been driven by the inclusion of anthracyclines in the neoadjuvant setting.
- 6.19 The results of tpCR in PEONY were similar to those in NEOSPHERE. Significantly more patients achieved tpCR in the Ptz+T+D group vs. the T+D group: 39.3% vs. 21.8%, difference = 17.5% (95% CI 6.9%, 28.0%). The tpCR rates in PEONY were determined by an IRC whereas in NEOSPHERE they were determined by local pathologists. The clinical complete response rates during the neoadjuvant period, were lower in PEONY: 11.0% in Ptz+T+D vs. 10.0% in T+D groups in PEONY, compared with 30.7% vs. 23.2% in NEOSPHERE. . It is unknown whether the smaller difference in clinical complete response observed in PEONY versus NEOSPHERE (1.0% in PEONY vs. 7.5% in NEOSPHERE) was due to a difference in trial design (i.e. open label in NEOSPHERE vs. double-blind in PEONY), or the use of a more stringent definition for complete response in PEONY, or both.¹⁰ Shao (2019) reported that at the data cut-off date for

⁹ TGA (2016) Australian Public Assessment Report (AusPAR) for Pertuzumab, p19.

¹⁰ Tumour response was evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.0 in NEOSPHERE and RECIST v1.1 in PEONY. There was a change of definition for complete response in RECIST v1.1. In RECIST v1.0, lymph nodes with respect to complete response were not addressed. In RECIST v1.1, complete response was defined as: for target lesions, disappearance of all target lesions, any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). For non-target lesions: disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). Non-complete response/non-progressive disease was defined as persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits (source: RECIST, available at: <http://www.irrecist.com/recist/recist-comparative/10.html>; accessed 6 January 2020).

primary efficacy analysis¹¹, survival outcomes were too limited to be presented as the follow-up period was short.

- 6.20 For the purposes of assessment of relative clinical effectiveness, patient-relevant survival outcomes, such as PFS, are more relevant than surrogate outcomes, such as bpCR and tpCR. Further, the relevance of the surrogate outcomes of bpCR and tpCR to survival outcomes, in particular for PFS and in the context of the availability of T-DM1, is uncertain. The PSCR argued that there is evidence that tpCR is associated with significantly reduced disease recurrence and overall survival¹². The ESC could not verify this claim based on Spring et al (2018) as only an abstract was available. The ESC noted that the PBAC framework for assessing a proposed surrogate measure was not addressed in the submission. The ESC considered that evidence from a pooled analysis of neoadjuvant trial data did not definitively link tpCR to patient relevant survival outcomes.¹³ The ESC also noted that Cortazar et al (2014) called for standardized definition of pCR as, at the individual level, eradication in nodes and breast was more strongly associated with survival outcomes than breast alone. The ESC noted that in NEOSPHERE the primary outcome was bpCR. The ESC considered that, despite indication of a patient-level association, bpCR was not adequately established as a relevant trial-level surrogate for survival outcomes.
- 6.21 The PSCR claimed that the PBAC's acceptance of the rationale for the KATHERINE trial (targeting patients without tpCR) and recommendation of T-DM1 validates the assumption that tpCR is an important surrogate outcome. The ESC noted that T-DM1 was recommended for patients without tpCR on the basis of a significant improvement in iDFS over trastuzumab and an indication that the iDFS results would translate into OS benefits based on the KATHERINE trial data, which only included patients without tpCR.
- 6.22 The three randomised trials were stratified by disease category (operable or early breast cancer, locally advanced breast cancer) and hormone receptor status (oestrogen receptor (ER) and/or progesterone receptor (PR) negative, ER- and/or PR-positive). Table 6 presents the bpCR subgroup results for the NEOSPHERE trial. Table 7 presents the tpCR results for PEONY. In both NEOSPHERE and PEONY, the treatment effect of Ptz+T+D was greater in the ER- and PR-negative subgroup vs. the ER- and/or PR-positive subgroup. Further, in both trials there was no evidence of a treatment effect for the ER- and/or PR-positive subgroup, even though the sample size was

¹¹ The primary efficacy objective of PEONY was to evaluate the IRC-determined tpCR rates. The primary efficacy analysis occurred when all patients who were eligible for surgery had completed surgical treatment with the assessment of pathological response (i.e. after neoadjuvant treatment and surgery) (p3, Protocol YO28762, Version 4, December 2016).

¹² Spring L, et al.: Pathological complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival, stratified by breast cancer subtypes and adjuvant chemotherapy usage. 2018 San Antonio Breast Cancer Symposium. Abstract GS2-03. Presented December 5, 2018.

¹³ Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *The Lancet*. 2014;384(9938):164-72.

reasonable, with these patients comprising about half of all patients in the two trials. In NEOSPHERE, the only comparative trial with relevant PFS data, the difference in PFS in this subgroup was not statistically significantly different (hazard ratio 0.86, 95% CI 0.27, 2.75).¹⁴ These results suggest that the addition of pertuzumab to T+D may not increase the effectiveness of the intervention in patients with ER- and/or PR-positive disease.

- 6.23 In PEONY, the treatment benefit of Ptz+T+D appeared to be greater among premenopausal women: the difference in IRC-determined tpCR rates was 22.5% (95% CI 9.9%, 35.1%) in the premenopausal subgroup vs. 10.3% (95% CI –8.2%, 28.9%) in the postmenopausal subgroup. Corresponding data from NEOSPHERE were not available.

Table 6: Pathological complete response in the breast (bpCR) in NEOSPHERE (ITT population)

| | Arm B (Ptz+T+D) n/N (%) | Arm A (T+D) n/N (%) | RR (95% CI) | Difference (Arm B – Arm A) % (95% CI), p-value |
|---|-------------------------------|---------------------------|----------------|--|
| Achieved pCR in the breast (bpCR) | 49/107 (45.8) | 31/107 (29.0) | 1.6 (NR) | 16.8 (3.5, 30.1) , p=0.0141* |
| Achieved pCR and node negative (tpCR) | 42/107 (39.3) | 23/107 (21.5) | 1.8 (NR) | 17.8 (4.6, 31.0) , p=0.008 [^] |
| Achieved pCR and node positive | 7/107 (6.5) | 8/107 (7.5) | 0.9 (NR) | -1.0 (-10.2, 8.2), p=0.83 [^] |
| Subgroups by BC type | | | | |
| Operable BC (T2-3a, N0-1, M0) | 31/65 (47.7) | 15/64 (23.4) | 2.0 (NR) | 24.3 (7.4, 41.1) |
| LABC (T3b-4c, N2-3, M0) | 14/32 (43.8) | 15/36 (41.7) | 1.1 (NR) | 2.1 (-23.4, 27.6) |
| iBC (T4d, any N, M0) | 4/10 (40.0) | 1/7 (14.3) | 2.8 (NR) | 25.7 (-24.0, 75.4) |
| Subgroups by hormone-receptor status | | | | |
| ER- and/or PR-positive | 13/50 (26.0) | 10/50 (20.0) | 1.3 (NR) | 6.0 (-11.6, 23.6) |
| ER- and PR-negative | 36/57 (63.2) | 21/57 (36.8) | 1.7 (NR) | 26.3 (7.6, 45.1) |

Source: Table 2.17, p57 of the submission; Tables 14, 16-17, pp91-93 in Primary CSR WO20697 (Report No. 1032196);

BC = breast cancer; bpCR = pCR in the breast; CI = confidence interval; D = docetaxel; eBC = early BC; ER = oestrogen receptor; iBC = inflammatory BC; ITT = intention-to-treat; LABC = locally advanced BC; n = number of participants with event; N = total participants in group; NR = not reported; Ptz = pertuzumab; PBO = placebo; pCR = pathological complete response; PR = progesterone receptor; RR = rate ratio; T = trastuzumab; tpCR = total pathological complete response

Bold indicates statistically significant results.

*p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment

[^] The submission reported that these results were calculated post-hoc and not adjusted for multiplicity (p57 of the submission).

Rate ratios were computed by simply dividing the pCR rates in the two treatment groups (Arm B vs. Arm A).

¹⁴ Page 154 in Final CSR WO20697 (Report No. 1062325).

Table 7: Total pathological complete response (tpCR) by subgroups in PEONY (not presented in the submission)

| | Ptz+T+D n/N (%) | Placebo+T+D n/N (%) | RR (95% CI) | Difference % (95% CI), p-value |
|---|--------------------|------------------------|--------------------------|-----------------------------------|
| tpCR-IRC | 86/219 (39.3) | 24/110 (21.8) | 1.80 (1.22, 2.66) | 17.5 (6.9, 28.0), p=.001 |
| Subgroups by BC type | | | | |
| eBC (T2-3, N0-1, M0) | 63/153 (41.2) | 20/77 (26.0) | 1.59 (1.04, 2.42) | 15.2 (2.0, 28.4) |
| LABC (T2-3, N2-3, M0) | 23/66 (34.8) | 4/33 (12.1) | 2.88 (1.08, 7.63) | 22.7 (5.0, 40.4) |
| Subgroups by hormone-receptor status | | | | |
| ER- and/or PR-positive | 39/117 (33.3) | 14/56 (25.0) | 1.33 (0.79, 2.25) | 8.3 (-6.9, 23.5) |
| ER- and PR-negative | 47/102 (46.1) | 10/54 (18.5) | 2.49 (1.37, 4.52) | 27.6 (12.4, 42.8) |
| Subgroups by lymph node status | | | | |
| Node positive | 55/160 (34.4) | 16/89 (18.0) | 1.91 (1.17, 3.13) | 16.4 (4.9, 27.9) |
| Node negative | 31/59 (52.5) | 8/21 (38.1) | 1.38 (0.76, 2.50) | 14.5 (-12.8, 41.7) |
| Subgroups by ERBB2 IHC | | | | |
| ERBB2 IHC2+ | 23/65 (35.4) | 6/22 (27.3) | 1.30 (0.61, 2.77) | 8.1 (-16.5, 32.8) |
| ERBB2 IHC3+ | 63/152 (41.4) | 18/88 (20.5) | 2.03 (1.29, 3.19) | 21.0 (8.9, 33.1) |
| Subgroups by menopausal status | | | | |
| Pre-menopausal | 48/132 (36.4) | 9/65 (13.8) | 2.63 (1.38, 5.02) | 22.5 (9.9, 35.1) |
| Post-menopausal | 38/87 (43.7) | 15/45 (33.3) | 1.31 (0.81, 2.11) | 10.3 (-8.2, 28.9) |
| Subgroups by | | | | |
| Chinese | 75/193 (38.9) | 20/99 (20.2) | 1.92 (1.25, 2.96) | 18.7 (7.6, 29.7) |
| Others | NR | NR | NR | NR |

Source: Shao (2019) for PEONY.

BC = breast cancer; CI = confidence interval; D = docetaxel; eBC = early BC; ER = oestrogen receptor; ERBB2 = human epidermal receptor growth factor 2; iBC = inflammatory BC; IHC = immunohistochemistry; LABC = locally advanced BC; n = number of participants with event; N = total participants in group; NR = not reported; Ptz = pertuzumab; PR = progesterone receptor; RR = rate ratio; T = trastuzumab; tpCR = total pathological complete response; tpCR-IRC = tpCR as determined by an Independent Review Committee (IRC)

Bold indicates statistically significant results.

RR and 95% Clin PEONY were not reported in Shao (2019) but were calculated using the raw data reported in Shao (2019) and the same methodology as used in the paper during the evaluation.

Comparative harms

6.24 One patient in the Ptz+T+D group in NEOSPHERE died during the neoadjuvant period and the death (fulminant hepatitis) was considered related to treatment. Shao (2019) reported that at the data cut-off date, there was one death in the Ptz+T+D group in PEONY: suicide on day 15 which was not considered as related to the study medications. Table 8 and Table 9 present serious adverse events (SAEs) and common adverse events (AEs) grade ≥ 3 respectively by treatment period for NEOSPHERE and TRYPHAENA. Table 10 presents the results for PEONY. The submission reported that the safety of Ptz+T+D was comparable to that of T+D in NEOSPHERE. Nine patients (8.4%) in the Ptz+T+D group experienced left ventricular systolic dysfunction or congestive heart failure (any grade) compared with two patients (1.9%) in the T+D group in NEOSPHERE.¹⁵ In addition, significantly more patients in the Ptz+T+D group experienced diarrhoea and infusion-related reactions in PEONY (Table 10). The claim of non-inferior comparative safety was considered uncertain during the evaluation.

¹⁵ Table 2.36, p73 of the submission.

6.25 The most common grade ≥ 3 AEs observed were docetaxel-related neutropenia, febrile neutropenia and leukopenia (Table 9). The TYPHAENA safety study demonstrated that six cycles of Ptz+T in combination with either anthracycline-based or carboplatin-based neoadjuvant chemotherapy was well tolerated with low rates of cardiac AEs (p85 of the submission). In PEONY, more patients in the Ptz+T+D group had the SAE of neutropenia (38.1% vs. 32.7%), significantly more had diarrhoea (38.5% vs. 16.4%) and infusion-related reactions (22.0% vs. 9.1%).

Table 8: Summary of serious adverse events (SAEs) by treatment period in NEOSPHERE and TRYPHAENA

| SAE | NEOSPHERE | | TRYPHAENA | |
|-------------------------------|-----------------------------------|-------------------------------|---|---|
| | Arm B (Ptz+T+D) n (%), n/N) | Arm A (T+D) n (%), n/N) | Arm A (Ptz+T+FEC) x3 → (Ptz+T+D) x3 n (%), n/N) | Arm C (Ptz+T+C+D) x6 n (%), n/N) |
| Neoadjuvant period | N=107 | N=107 | N=72 | N=76 |
| Patients with ≥ 1 event | 11 (10.3) | 18 (16.8) | 20 (27.8) | 27 (35.5) |
| Febrile neutropenia | 6 (5.6) | 7 (6.5) | 10 (13.9) | 11 (14.5) |
| Neutropenia | 4 (3.7) | 1 (0.9) | NR | NR |
| Diarrhoea | NR | NR | 1 (1.4) | 4 (5.3) |
| Total number of events | 15 | 20 | 27 | 39 |
| Adjuvant period | N=102 | N=103 | N=68 | N=67 |
| Patients with ≥ 1 event | 11 (10.8) | 5 (4.9) | 5 (7.4) | 6 (9.0) |
| Febrile neutropenia | 2 (2.0) | 3 (2.9) | NR | NR |
| Total number of events | 15 | 5 | 5 | 0 |
| Total treatment period | N=107 | N=107 | N=72 | N=76 |
| Patients with ≥ 1 event | 22 (20.6) | 21 (19.6) | 23 (31.9) | 31 (40.8) |
| Febrile neutropenia | 8 (7.5) | 10 (9.3) | NR | NR |
| Neutropenia | 6 (5.6) | 1 (0.9) | NR | NR |
| Total number of events | 31 | 25 | NR | NR |

Source: Tables 2.34 and 2.40, pp72 and 78 of the submission

C = carboplatin; D = docetaxel; FEC = 5-fluorouracil, epirubicin and cyclophosphamide; n = number of participants with event; N = total participants in group; Ptz = pertuzumab; T = trastuzumab

Table 9: Summary of adverse events (AEs) of severity CTCAE grade ≥3 in ≥3% of patients by treatment period in NEOSPHERE and TRYPHAENA

| CTCAE grade ≥3 AE | NEOSPHERE | | TRYPHAENA | |
|-------------------------------|-----------------------------------|-------------------------------|--|--|
| | Arm B (Ptz+T+D) n (% , n/N) | Arm A (T+D) n (% , n/N) | Arm A (Ptz+T+FEC) x3 → (Ptz+T+D) x3 n (% , n/N) | Arm C (Ptz+T+C+D) x6n n (% , n/N) |
| Neoadjuvant period | N=107 | N=107 | N=72 | N=76 |
| ≥1 AE grade ≥3 | 67 (62.6) | 78 (72.9) | 50 (69.4) | 56 (73.7) |
| Neutropenia | 48 (44.9) | 61 (57.0) | 34 (47.2) | 25 (46.1) |
| Febrile neutropenia | 9 (8.4) | 8 (7.5) | 13 (18.1) | 13 (17.1) |
| Diarrhoea | 6 (5.6) | 4 (3.7) | 3 (4.2) | 9 (11.8) |
| Leukopenia | 5 (4.7) | 13 (12.1) | 14 (19.4) | 9 (11.8) |
| Alopecia | 5 (4.7) | 1 (0.9) | NR | NR |
| ALT increased | 0 (0) | 3 (2.8) | 0 (0) | 3 (3.9) |
| Anaemia | NR | NR | 1 (1.4) | 13 (17.1) |
| Thrombocytopenia | NR | NR | 0 (0) | 9 (11.8) |
| Vomiting | NR | NR | 0 (0) | 4 (5.3) |
| Adjuvant period | N=102 | N=103 | N=68 | N=67 |
| ≥1 AE grade ≥3 | 36 (35.3) | 27 (35.9) | 9 (13.2) | 8 (11.9) |
| Neutropenia | 25 (24.5) | 23 (26.2) | 3 (4.4) | 1 (1.5) |
| Febrile neutropenia | 3 (2.9) | 3 (2.9) | NR | NR |
| Vomiting | 0 (0) | 3 (2.9) | NR | NR |
| Total treatment period | N=107 | N=107 | N=72 | N=76 |
| ≥1 AE grade ≥3 | 78 (72.9) | 87 (81.3) | 53 (73.6) | 56 (73.7) |
| Neutropenia | 59 (55.1) | 71 (66.4) | NR | NR |
| Febrile neutropenia | 12 (11.2) | 10 (9.3) | NR | NR |
| Leukopenia | 6 (5.6) | 13 (12.1) | NR | NR |
| Diarrhoea | 7 (6.5) | 4 (3.7) | NR | NR |
| Irregular menstruation | 4 (3.7) | 6 (5.6) | NR | NR |
| Vomiting | 0 (0) | 3 (2.8) | NR | NR |
| ALT increased | 0 (0) | 3 (2.8) | NR | NR |

Source: Tables 2.33 and 2.39, pp71 and 77 of the submission

AE = adverse event; ALT = Alanine aminotransferase; C = carboplatin; CTCAE = Common Terminology Criteria for Adverse Events; D = docetaxel; FEC = 5-fluorouracil, epirubicin and cyclophosphamide; n = number of participants with event; N = total participants in group; NR = not reported; Ptz = pertuzumab; T = trastuzumab

Data shaded in blue were used in the economic model.

Table 10: Serious and Grade ≥3 adverse events (AEs) in PEONY (safety population) (not presented in the submission)

| PEONY | (Ptz+T+D) x4 N=218 n (% , n/N) | (PBO+T+D) x4 N=110 n (% , n/N) |
|--|--------------------------------------|--------------------------------------|
| Deaths | 1 (0.5) | 0 (0) |
| SAE | 22 (10.1) | 9 (8.2) |
| Most common SAE: febrile neutropenia | 4 (1.8) | 1 (0.9) |
| Most common Grade ≥3 AEs (≥3% of patients) | | |
| Neutropenia | 83 (38.1) | 36 (32.7) |
| Leukopenia | 45 (20.6) | 21 (19.1) |
| Selected 10 most common AEs | | |
| Neutropenia | 105 (48.2) | 49 (44.5) |
| Leukopenia | 92 (42.2) | 43 (39.1) |
| Diarrhoea | 84 (38.5) | 18 (16.4) |
| Pyrexia | 31 (14.2) | 11 (10.0) |
| Infusion-related reactions | 48 (22.0) | 10 (9.1) |

Source: Shao (2019) for PEONY

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AE = adverse event; D = docetaxel; n = number of participants with event; N = total participants in group; Ptz = pertuzumab; PBO = placebo; SAE = serious adverse event; T = trastuzumab; **Bold** indicates statistically significant results.

Benefits/harms

6.26 A summary of the comparative benefits and harms for the addition of pertuzumab to T+Chemo versus the addition of placebo/nothing to T+Chemo is presented in Table 11.

Table 11: Summary of comparative benefits and harms for the addition of pertuzumab vs. the addition of placebo/nothing to (T+Chemo)*

| | Pertuzumab n/N | PBO/Nothing n/N | RR (95% CI) | Event rate/100 patients | | RD (95% CI) |
|---|-------------------|--------------------|--------------------------|----------------------------|-------------|-------------------------|
| | | | | Pertuzumab | PBO/Nothing | |
| Benefits | | | | | | |
| Pathological complete response in the breast after neoadjuvant treatment | | | | | | |
| NEOSPHERE | 49/107 | 31/107 | 1.58 (1.10-2.27) | 45.8 | 29.0 | 16.8 (3.5, 30.1) |
| Total pathological complete response after neoadjuvant treatment | | | | | | |
| NEOSPHERE | 42/107 | 23/107 | 1.83 (1.19, 2.81) | 39.3 | 21.5 | 17.8 (4.6, 31.0) |
| PEONY | 86/219 | 24/110 | 1.80 (1.22, 2.66) | 39.3 | 21.8 | 17.5 (6.9, 28.0) |
| Clinical complete response as best tumour response during neoadjuvant treatment period | | | | | | |
| NEOSPHERE | 31/101 | 23/99 | 1.32 (0.83, 2.10) | 30.7 | 23.2 | 7.5% (-5.4, 20.3) |
| PEONY | 24/219 | 11/110 | 1.10 (0.56, 2.15) | 11.0 | 10.0 | 1.0% (-6.5, 8.4) |
| Survival outcomes in NEOSPHERE (5 years from randomisation) | | | | | | |
| Progression free survival | | (Ptz+T+D) | (T+D) | Absolute Difference | | HR (95% CI) |
| Progressed, n (%) | | 17/107 (15.9) | 19/107 (17.8) | | | |
| % not progressed at 1 year (95% CI) | | 96% (92, 100) | 98% (95, 100) | -2% (NR) | | |
| % not progressed at 2 year (95% CI) | | 93% (88, 98) | 90% (84, 96) | 3% (NR) | | 0.69 |
| % not progressed at 5 years (95% CI) | | 86% (77, 91) | 81% (71, 87) | 5% (NR) | | (95% CI 0.34, 1.40) |
| Overall survival | | | | | | |
| Deaths, n/N (%) | | n/N (%) | n/N (%) | | | |
| Neoadjuvant treatment period | | 1/107 (0.9) | 0/107 (0) | | | |
| Adjuvant treatment period | | 0 (0) | 0 (0) | | | |
| Total treatment period | | 8/107 (7.5) | 6/107 (5.6) | | | |
| End of study (5 years from randomisation) | | 17/107 (15.9) | 19/107 (17.8) | | | |
| Harms (during neoadjuvant treatment period) | | | | | | |
| | Pertuzumab n/N | PBO/Nothing n/N | RR (95% CI) | Event rate/100 patients | | RD (95% CI) |
| | | | | Pertuzumab | PBO/Nothing | |
| AEs in NEOSPHERE | | | | | | |
| ≥1 SAE | 11/107 | 18/107 | 0.61 (0.30, 1.23) | 10.3 | 16.8 | -6.5% (-16.2, 3.1) |
| SAE-febrile neutropenia | 6/107 | 7/107 | 0.86 (0.30, 2.47) | 5.6 | 5.6 | 0.9% (-7.8, 6.0) |
| ≥1 AE of CTCAE grade ≥3 severity | 67/107 | 78/107 | 0.86 (0.71, 1.04) | 62.6 | 72.9 | -10.3% (-23.3, 2.7) |
| Neutropenia of CTCAE grade ≥3 severity | 48/107 | 61/107 | 0.79 (0.60, 1.03) | 44.9 | 57.0 | -12.1% (-26.0, 1.7) |
| Febrile neutropenia of CTCAE grade ≥3 severity | 9/107 | 8/107 | 1.13 (0.45, 2.81) | 8.4 | 7.5 | 0.9% (-6.8, 8.7) |
| Leukopenia of CTCAE grade ≥3 severity | 5/107 | 13/107 | 0.38 (0.14, 1.04) | 4.7 | 12.1 | -7.5% (-15.3, 0.4) |
| Diarrhoea of CTCAE grade ≥3 severity | 6/107 | 4/107 | 1.50 (0.44, 5.17) | 5.6 | 3.7 | 1.9% (-4.3, 8.0) |

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| | | | | | | |
|--|--------|--------|--------------------------|------|------|--------------------------|
| Left ventricular systolic dysfunction (any grade) (overall study period) | 9/107 | 2/107 | 4.50 (1.00, 20.34) | 8.4 | 1.9 | 6.5% (0.2, 12.9) |
| Common AEs in PEONY (as reported in Shao 2019) | | | | | | |
| Diarrhoea | 84/218 | 18/110 | 2.35 (1.49, 3.71) | 38.5 | 16.4 | 22.2 (12.2, 32.1) |
| Infusion-related reactions | 48/218 | 10/110 | 2.42 (1.28, 4.60) | 22.0 | 9.1 | 12.9 (4.8, 21.1) |

Source: Tables 2.20, 2.30-34, 2.36-2.37 and 2.42, pp58-59, 66-67, 69-73 and 79-80 of the submission; Shao (2019) for PEONY.

AE = adverse event; C = carboplatin; CTCAE = Common Terminology Criteria for Adverse Events; D = docetaxel; FEC = 5-fluorouracil, epirubicin and cyclophosphamide; HR = hazard ratio; IV = intravenous; NR = not reported; Ptz = pertuzumab; PBO = placebo; RD = risk difference; RR = risk ratio; SAE = serious adverse event; T = trastuzumab

* The comparator was adding nothing to T+Chemo in NEOSPHERE; whereas the comparator was adding pertuzumab-matching placebo IV in PEONY. T+Chemo referred to T+D for both NEOSPHERE and PEONY. T+Chemo in TRYPHAENA referred to either 3 cycles of FEC followed by 3 cycles of D (Arm A) or 6 cycles of C and D (Arm C).

Bold indicates statistically significant results.

6.27 On the basis of direct evidence presented by the submission, for every 100 patients treated with four cycles of Ptz+T+D in comparison to four cycles of T+D, in the neoadjuvant setting, approximately:

- 18 additional patients will achieve tpCR (PEONY).
- 22 additional patients will experience diarrhoea (PEONY).
- 13 additional patients will experience infusion-related reactions (PEONY).
- 7 additional patients will experience left ventricular systolic dysfunction (any grade) (NEOSPHERE).

Clinical claim

6.28 The submission described Ptz+T+Chemo as superior to T+Chemo in terms of comparative effectiveness (p85 of the submission). The ESC considered that this claim was not adequately supported by the evidence presented:

- Although the addition of pertuzumab significantly improved bpCR in both NEOSPHERE and PEONY, the relevance of this surrogate to OS and PFS is uncertain, particularly in the context of T-DM1. At the November 2019 meeting, the PBAC 'noted that the availability of T-DM1 in the adjuvant setting would change the treatment algorithm and improve patient outcomes. The PBAC considered that any future submissions for therapies for HER2+ eBC would need to account for the availability and efficacy of T-DM1 and demonstrate benefit in a treatment algorithm that includes T-DM1' (para 7.3, trastuzumab emtansine, Public Summary Document, November 2019). The submission did not demonstrate that sequential pertuzumab and T-DM1 is superior to T-DM1. The ESC noted that the population eligible for T-DM1 may be up to half the patients eligible for pertuzumab. The ESC further noted that the KATHERINE trial included some patients (18%) who were treated with neoadjuvant pertuzumab and considered this trial could provide context regarding sequential use of pertuzumab and T-DM1.

- For the pCR outcomes, a 15% difference was nominated as the minimal clinically important difference (MCID). The ESC considered that the MCID was not adequately justified and noted that the lower 95% confidence intervals of the differences in tpCR of 6.9% in PEONY and 4.6% in NEOSPHERE were substantially lower than the MCID of 15%. In addition, the ESC considered there was not strong evidence to support the use of a change in bpCR as a surrogate for a change in PFS or OS.
 - The ESC noted that anthracyclines are a key component of neoadjuvant chemotherapy in clinical practice as they improve pCR rates as acknowledged in the pre-PBAC response. However, anthracycline-based regimens in the neoadjuvant setting were not permitted in NEOSPHERE or PEONY and were instead given in the adjuvant setting. Thus, the ESC considered that it was uncertain whether the results from the trials would be reflective of clinical outcomes in practice.
 - An improvement in PFS or DFS was not demonstrated (NEOSPHERE PFS HR=0.69, 95% CI 0.34, 1.40; DFS HR=0.60, 95% CI 0.28, 1.27).
 - The submission described Ptz+T+Chemo as non-inferior to T+Chemo in terms of comparative safety. This claim was considered uncertain during the evaluation. Nine patients (8.4%) in the Ptz+T+D group experienced left ventricular systolic dysfunction or congestive heart failure (any grade) compared with two patients (1.9%) in the T+D group in NEOSPHERE. In addition, significantly more patients in the Ptz+T+D group experienced diarrhoea and infusion-related reactions in PEONY (Table 10).
 - In NEOSPHERE and PEONY there was no evidence of a treatment effect for the estrogen-receptor- and/or progesterone-receptor -positive subgroup.
- 6.29 The PBAC considered that the claims of superior comparative effectiveness and non-inferior comparative safety of Ptz+T+Chemo versus T+Chemo were not adequately supported by the data.

Economic analysis

- 6.30 The submission presented a cost-utility model comparing Ptz+T+Chemo to usual care, defined as T+Chemo. The evaluation was based on the PFS data from the NEOSPHERE clinical trial, Australian life tables and published sources.
- 6.31 Table 12 summarises the key components of the economic evaluation.

Table 12: Summary of model structure, key inputs and rationale

| Component | Summary |
|----------------------------------|---|
| Treatments | Pertuzumab + trastuzumab + chemotherapy (Ptz+T+Chemo) vs trastuzumab + chemotherapy (T+Chemo) |
| Time horizon | 40 years versus 5.1 years in the NEOSPHERE trial |
| Outcomes | Life years and QALYs gained |
| Methods used to generate results | Markov model, tapered treatment effect, sustained remission adjustment |
| Health states | Six health states (PFS, locoregional recurrence, remission, metastatic recurrence (1st line mBC and 2nd line mBC), death). Metastatic recurrence is stratified by time to relapse (<18 months or ≥18 months). PFS is stratified by on/off treatment. |
| Cycle length | One week |
| Transition probabilities | PFS to locoregional recurrence, metastatic recurrence, and death from NEOSPHERE clinical trial. Locoregional recurrence to remission is a 12 month tunnel state. Remission to metastatic recurrence from Hamilton (2015). Metastatic recurrence to progression (1 st line to 2 nd line) and death from EMILIA and CLEOPATRA clinical trials. |
| Extrapolation method | Kaplan-Meier data was used for PFS until median follow up (60.8 months) then independent exponential models were fitted to each treatment arm based on goodness of fit. Mortality from PFS, locoregional recurrence and remission was the greater of general population mortality and PFS death events from NEOSPHERE trial. Disease progression and survival from metastatic recurrence were applied as constant weekly transition probabilities derived from extrapolations of EMILIA and CLEOPATRA trial data. A time-dependent treatment effect was included by gradually adjusting the PFS transition probability for Ptz+T+Chemo between Year 7 and Year 10. At ten years, the PFS transition probability for Ptz+T+Chemo = T+Chemo. Convergence of PFS curves is not reached within the 40 year time horizon. A sustained remission adjustment was applied from median follow up, increasing to 95% at ten years. 98% of QALYs, 98% LYs gained occurred in the extrapolated period. |
| Health-related quality of life | No utility data were collected in the NEOSPHERE trial. The APHINITY trial was used for utility values for PFS, locoregional recurrence & remission. Lloyd (2006) was used for utility values for metastatic recurrence. PFS on treatment = 0.784, PFS off treatment = 0.828, locoregional recurrence = 0.784, remission 0.828, 1 st line mBC = 0.753, 2 nd line mBC = 0.481. |
| Trastuzumab dosing in PFS | The model applied the average actual dose of trastuzumab observed overall in the NEOSPHERE trial, multiplied by the proportion of patients remaining on treatment. |

Source: Tables 3.2, 3.6, 3.8, 3.15 & 3.21, p88, 97-98, 107, 116 & 119, and Section 3.4 of the submission.

QALY = quality adjusted life year, mBC = metastatic breast cancer, PFS = progression free survival, P+T+C = pertuzumab + trastuzumab + chemotherapy, T+C = trastuzumab + chemotherapy

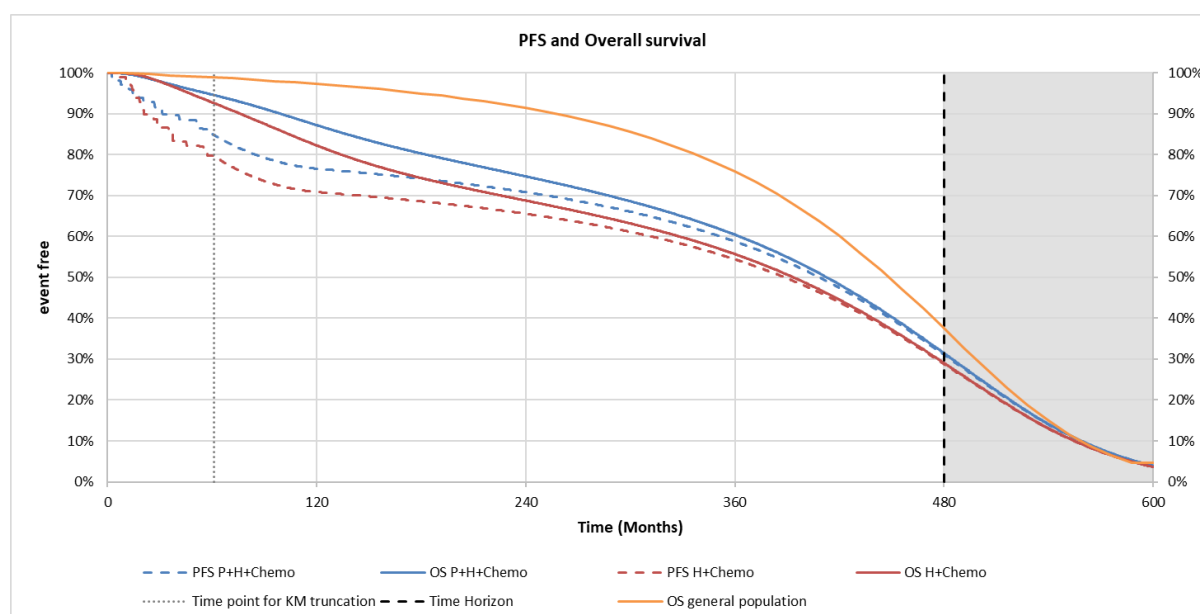
6.32 The model comprised six health states (PFS, locoregional recurrence, remission, 1st line metastatic recurrence, 2nd line metastatic recurrence, and death). The PFS health state included neoadjuvant treatment with Ptz+T+Chemo or T+Chemo, primary surgery, and adjuvant treatment with T+Chemo. While this ensures consistency with the NEOSPHERE trial, the model structure does not reflect the breast cancer treatment algorithm proposed in the clinical section, where HER2+ early breast cancer patients with residual disease following surgery receive adjuvant treatment with T-DM1. The model does not allow for the different transition probabilities, utilities and costs associated with the different adjuvant treatments available in Australia (trastuzumab and T-DM1). The evaluation and ESC considered that a model structure that considers

adjuvant treatment with T-DM1, separating the neoadjuvant and adjuvant phases of treatment, may be preferable. NEOSPHERE could inform the probability of pCR following surgery.

- 6.33 The PSCR and pre-PBAC response argued that it would be challenging to update the economic model to incorporate adjuvant treatment with T-DM1 since there is no clinical trial that has investigated neoadjuvant Ptz+T+Chemo followed by adjuvant T-DM1. Additionally, the PSCR stated that adjuvant T-DM1 is intended for use in only a small proportion of patients with a specific type of early breast cancer and modelling such a specific population would not be expected to inform the current decision problem. The ESC disagreed with the PSCR, noting the following:
- The submission claimed that neoadjuvant pertuzumab would reduce downstream use of T-DM1 and therefore the associated costs and benefits of T-DM1 should be accounted for in the economic model;
 - Modelling the use of adjuvant T-DM1 is relevant due to the overlap of the PBS restrictions for neoadjuvant pertuzumab and adjuvant T-DM1;
 - The proposed treatment algorithm and financial estimates in the submission suggest that a substantial proportion of patients eligible for adjuvant pertuzumab would also be eligible for adjuvant T-DM1; and
 - Although there is no clinical trial specifically investigating neoadjuvant Ptz+T+Chemo followed by adjuvant T-DM1, it may be possible to use data from the KATHERINE trial to inform an economic model including adjuvant T-DM1.
- 6.34 Modelled PFS was derived from the NEOSPHERE trial. PFS was a secondary endpoint, not powered to test formal hypotheses. The result is uncertain, with the 95% confidence interval crossing unity by a wide margin (hazard ratio = 0.69, 95% CI (0.34, 1.40). As the incremental gain in PFS is the key driver of the ICER, the ICER is highly uncertain.
- 6.35 Extrapolation of PFS was conducted in three stages: first, parametric extrapolation of Kaplan-Meier data observed in NEOSPHERE, then application of a time limited treatment effect to PFS, and finally application of a sustained remission adjustment (cure fraction) for a proportion of patients remaining in PFS. The assumptions regarding treatment effect waning and sustained remission adjustment were uncertain but had minimal impact on the ICER.
- 6.36 PFS was extrapolated from the median follow up (5.1 years) to the 40 year time horizon using independent exponential functions. Although six parametric survival functions were fitted to PFS data, only four were presented in the submission. The sponsor stated that the gamma and Gompertz functions were excluded as they produced erroneous results due to the low patient numbers and observed events. As 98% of QALYs were accrued in the extrapolated period, uncertainty in the extrapolation of PFS was a key issue.

- 6.37 Survival from PFS, locoregional recurrence and remission was the lesser of the pooled PFS death events recorded in NEOSPHERE and age-specific background mortality. Survival for patients experiencing early metastatic recurrence was the lesser of survival observed in EMILIA and age-specific background mortality. Survival for patients experiencing late metastatic recurrence was the lesser of survival observed in CLEOPATRA and age-specific background mortality. The evaluation considered this approach was reasonable.
- 6.38 Figure 3 presents modelled PFS and OS for Ptz+T+Chemo and T+Chemo over the 40 year time horizon.

Figure 3: Modelled PFS and OS for patients treated with Ptz+T+Chemo and T+Chemo



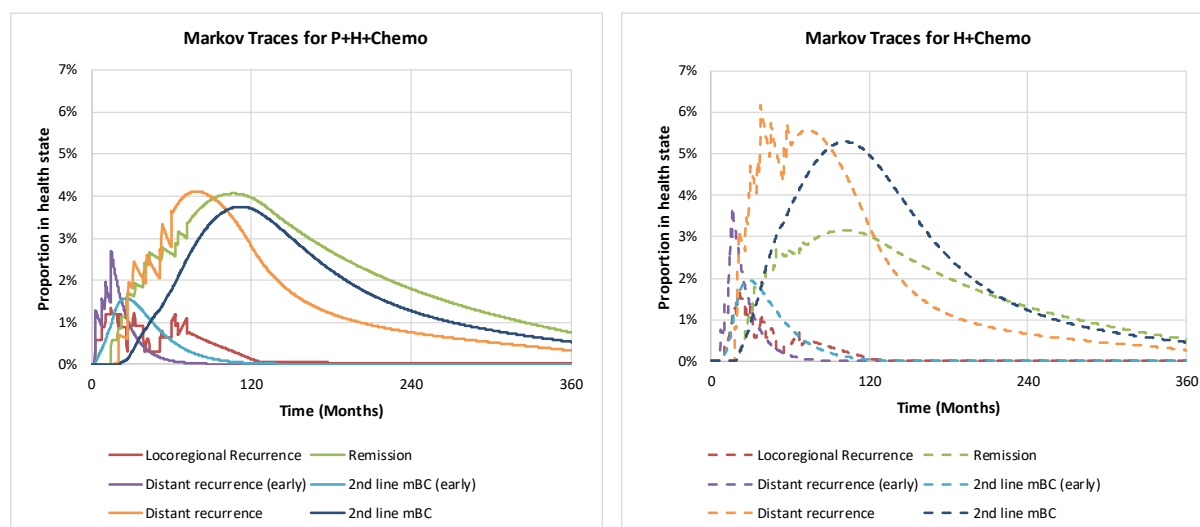
Source: Figure 3.11, p114 of the submission, OS for general population added during the evaluation. OS = overall survival; PFS = progression free survival; Ptz+T+Chemo = pertuzumab + trastuzumab + chemotherapy; T+Chemo = trastuzumab + chemotherapy

- 6.39 The mean starting age of patients in the model is 50.2 years. This was taken from NEOSPHERE. At the 40-year time horizon, modelled patients will be 90.2 years old, at which time the model predicts approximately 30% of patients in each arm are alive and free of disease progression (Figure 3). Figure 3 shows that modelled PFS and OS for patients with early breast cancer are less than general population survival.
- 6.40 Given the immaturity of PFS, instead of extrapolating PFS directly, it may be preferable to extrapolate PFS based on a surrogate relationship between pCR and PFS and OS, if such relationships exist. Within this framework, it may be possible to model adjuvant treatment with T-DM1. The PSCR argued that this approach produced illogical results that did not make it possible to reliably model outcomes of neoadjuvant treatment. The ESC noted the sponsor did not articulate the issues encountered with the analysis or in what sense the results were ‘illogical’. The ESC considered that this approach would require further justification of the proposed surrogate relationship between the change in pCR and the change in survival outcomes. The ESC noted that such a

model would better reflect the proposed clinical place of pertuzumab but it is unclear whether such an analysis would provide additional certainty with regards to the modelled outcomes.

- 6.41 Predicted population sizes over time by health state are presented in Figure 4. Of patients experiencing disease recurrence, 81% in the T+Chemo arm experienced distant recurrence, compared with 69% in the Ptz+T+Chemo arm. More patients receiving T+Chemo than Ptz+T+Chemo were predicted to experience distant recurrence (1st line metastatic breast cancer) and remain in the costly 1st line and 2nd line metastatic breast cancer health states.

Figure 4: Modelled post-progression health state occupancy



Source: Adapted from Figure 3.12, p115 of the submission

H + Chemo = trastuzumab (Herceptin) + chemotherapy; mBC = metastatic breast cancer; P+H+Chemo = pertuzumab + trastuzumab (Herceptin) + chemotherapy.

- 6.42 The ESC noted that the choice of functional form for extrapolation had a relatively small impact on the ICER, however the ESC considered that other factors in the model could be masking the sensitivity to the extrapolation methods.
- 6.43 Utility data were not collected in NEOSPHERE. The submission considered data from the APHINITY trial, comparing utility in PFS on/off treatment for Ptz+T+Chemo and T+Chemo in the adjuvant setting, most representative of the corresponding data in the neoadjuvant setting. APHINITY utilities for PFS on/off treatment were used as a proxy for the locoregional recurrence and remission health states. A literature search revealed a study, Lloyd (2006), which informed utilities for the metastatic health states and sensitivity analyses. The ESC agreed with the commentary that the utilities appear reasonable, though they were drawn from different sources. The ICER is affected only marginally by plausible variations in utilities.
- 6.44 The submission incorrectly calculated the cost of trastuzumab by multiplying the average dose (allowing for discontinuations) received per cycle by the proportion of patients remaining on treatment. This double-counted patients who discontinue

treatment. When the planned dose of trastuzumab is multiplied by the proportion of patients remaining on treatment, the ICER increased from less than \$15,000 to less than \$15,000/QALY. The PSCR acknowledged this error and agreed with the corrected values.

6.45 Table 13 presents the key drivers of the economic model.

Table 13: Key drivers of the model

| Description | Method/Value | Impact Base case ICER: \$ [redacted] /QALY gained. |
|---------------------------------|--|--|
| Observed PFS benefit | The model applied observed PFS from NEOSPHERE until median follow-up (60.8 months). PFS is a secondary endpoint and not powered to test formal hypotheses. The ESC considered the PFS results to be highly uncertain, with the 95% confidence interval crossing unity by a wide margin (hazard ratio = 0.69, 95% CI (0.34, 1.40)). | Highly uncertain. |
| Parametric extrapolation of PFS | PFS is extrapolated from median follow-up (5.1 years) to 40 years using independent exponential functions. Six parametric survival functions were fitted to observed data, two functions (gamma and Gompertz) produced results which do not appear to be clinically plausible. The sponsor stated this was due to low patient numbers and observed events. Low patient numbers and observed events generate uncertainty in all extrapolated functions. | Highly uncertain. |
| Duration of treatment for mBC | The duration of treatment with trastuzumab, pertuzumab and trastuzumab emtansine are based on an existing risk share arrangement in the metastatic setting. Applying the duration of treatment observed in the DUSC report ¹⁶ reduced the cost of subsequent treatment. | Moderate, favours Ptz+T+Chemo. |
| Costs in mBC | The model predicted less time spent per patient in mBC averaged over all patients in the Ptz+T+Chemo arm compared to T+Chemo arm. Also, the cost of treatment in 1 st -line BC was assumed 100% pertuzumab, so this health state is associated with high costs. | Uncertain, favours Ptz+T+Chemo. |
| Trastuzumab cost calculations | The submission incorrectly calculated the cost of trastuzumab by multiplying the average dose received (allowing for discontinuations) per cycle by the proportion of patients remaining on treatment. This double-counted patients who discontinue treatment. | Moderate, favours Ptz+T+Chemo. Correcting this error increased the ICER to \$ [redacted] /QALY. |

Source: Tables 2.7 & 2.20, pp45 & 59 of the submission, Figure 3.11, p114 of the submission, p98 of the submission, communication with the sponsor during the evaluation, sheet 'Drug Doses & Acquisition Costs' of the Economic Evaluation workbook.

IPD = individual patient data, PFS = progression free survival; Ptz+T+Chemo = pertuzumab + trastuzumab + chemotherapy; T+Chemo = trastuzumab + chemotherapy

6.46 Table 14 presents the results of the stepped economic evaluation using the re-specified base case (prescribed dose of trastuzumab in NEOSPHERE, multiplied by patients remaining on treatment). Step 2 extended the time horizon from 5.1 to 40 years and the ICER reduced substantially, from more than \$200,000 to less than \$15,000 per life year gained. Extrapolation accounts for 98.5% $(1-0.013/0.867)*100$ of the estimated gain in incremental life years. The ESC agreed with the commentary

¹⁶ DUSC (February 2018) Medicines for the treatment of HER2 positive metastatic breast cancer: predicted versus actual analysis

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that the ICER is highly uncertain as almost all of the benefit is extrapolated and is based on the (non-significant) difference in PFS in NEOSPHERE.

Table 14: Results of the stepped economic evaluation – respecified base case

| Step and component | Ptz+T+Chemo | T+Chemo | Increment |
|--|---------------|---------------|---------------|
| Step 1: trial-based costs and outcomes | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG | 4.271 | 4.259 | 0.013 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 2: time horizon extended to 40 years | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG | 13.780 | 12.913 | 0.867 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 3: time limited treatment effect | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG | 13.618 | 12.913 | 0.705 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 4: sustained remission adjustment | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG | 14.748 | 14.079 | 0.669 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 5: incorporate medical resource use costs | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG | 14.748 | 14.079 | 0.669 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 6: incorporate adverse event costs | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG | 14.748 | 14.079 | 0.669 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 7: incorporate end of life costs | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG | 14.748 | 14.079 | 0.669 |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Step 8: incorporate utility values to determine QALYs | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALY | 11.956 | 11.369 | 0.588 |
| Incremental cost/extra QALY gained (base case) | | | \$ [REDACTED] |

Source: Tables 3.15 to 3.21, pp116-119 of the submission. Adapted using the corrected dose of trastuzumab in each treatment arm.
 LY = life year; LYG = life years gained; QALY = quality adjusted life years; Ptz+T+Chemo = pertuzumab + trastuzumab + chemotherapy;
 T+Chemo = trastuzumab + chemotherapy

6.47 The number of recurrence events over the 60.8 month trial follow-up period and 40-year modelled time horizon are compared in Table 15. Over the 40-year time horizon, each patient treated with pertuzumab in addition to trastuzumab and chemotherapy gained an average of 1.69 life years (169.44 per 100 patients, undiscounted). There were 29.7 (169.44/5.9) life years gained per metastatic recurrence avoided. As survival from the metastatic health states was derived from the EMILIA and CLEOPATRA trials rather than NEOSPHERE, there is considerable uncertainty in this estimate.

Table 15: Recurrence events (undiscounted)

| Outcome | Ptz+T+Chemo | T+Chemo | Incremental outcome (per 100 patients) |
|---|-------------|---------|---|
| LY (40 years, undiscounted) | 29.06 | 27.34 | 1.69 per patient (169.44 per 100 patients) |
| Locoregional recurrence | | | |
| Trial locoregional recurrence (60.8 months) | 3.9% | 3.4% | 0.5 |
| Model locoregional recurrence (40 years) | 7.2% | 5.5% | 1.8 |
| Metastatic recurrence | | | |
| Trial metastatic recurrence (60.8 months) | 9.5% | 15.3% | -5.8 |
| Model metastatic recurrence (40 years) | 22.6% | 28.5% | -5.9 |
| Any recurrence | | | |
| Trial any recurrence (60.8 months) | 13.4% | 18.7% | -5.3 |
| Model any recurrence (40 years) | 29.8% | 33.9% | -4.1 |

Source: Table 3.14, p115 of the submission, sheet 'Results' of Economic Evaluation workbook.

LY = life years; Ptz+T+Chemo = pertuzumab + trastuzumab + chemotherapy; T+Chemo = trastuzumab + chemotherapy

6.48 Table 16 presents the disaggregated QALYs from the economic evaluation. Additional QALYs gained in PFS account for 112% of total incremental QALYs. Fewer QALYs gained in metastatic disease (1st line and 2nd line metastatic breast cancer) account for 15% and 10% of total QALYs.

Table 16: Disaggregated summary of QALYs

| Outcome – QALYs | Pertuzumab + trastuzumab | Trastuzumab | Incremental | % of total incremental |
|--------------------------|--------------------------|-------------|-------------|------------------------|
| PFS | 11.19 | 10.53 | 0.66 | 112% |
| Locoregional recurrence | 0.04 | 0.03 | 0.01 | 2% |
| Remission | 0.32 | 0.25 | 0.07 | 12% |
| 1 st line mBC | 0.25 | 0.34 | -0.09 | -15% |
| 2 nd line mBC | 0.16 | 0.22 | -0.06 | -10% |
| Total | 11.96 | 11.37 | 0.59 | 100% |

Source: sheet 'Results' of the Economic Evaluation workbook

PFS = progression free survival; mBC = metastatic breast cancer.

6.49 Table 17 presents the disaggregated costs from the economic evaluation. The cost of neoadjuvant pertuzumab in addition to trastuzumab accounts for an additional less than \$10 million per patient. Cost offsets due to reduced use of subsequent treatments for metastatic disease (1st line and 2nd line metastatic breast cancer) are predicted to be substantial, less than \$10 million and less than \$10 million per patient respectively. The ESC considered it was reasonable to include costs and QALYs for metastatic breast cancer, but that the incremental costs and QALYs were based on highly uncertain extrapolated treatment effect and appear overestimated.

Table 17: Disaggregated summary of costs – respecified base case

| Resource item | Pertuzumab + trastuzumab | Trastuzumab | Incremental | % of total incremental |
|---|--------------------------|---------------|----------------|------------------------|
| Pharmaceutical products | | | | |
| PBS medicine | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | 219% |
| Administration cost | \$ [REDACTED] | \$ [REDACTED] | -\$ [REDACTED] | -1% |
| Total | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | 218% |
| Medical services | | | | |
| CT scan, LVEF assessment, specialist visit, pathology | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | 0% |
| Management of adverse events | | | | |
| Cost of adverse events | \$ [REDACTED] | \$ [REDACTED] | -\$ [REDACTED] | -9% |
| Subsequent treatments | | | | |
| Locoregional recurrence | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | 8% |
| 1 st line mBC | \$ [REDACTED] | \$ [REDACTED] | -\$ [REDACTED] | -72% |
| 2 nd line mBC | \$ [REDACTED] | \$ [REDACTED] | -\$ [REDACTED] | -44% |
| End of life (palliative care) | \$ [REDACTED] | \$ [REDACTED] | -\$ [REDACTED] | -1% |
| Total | \$ [REDACTED] | \$ [REDACTED] | -\$ [REDACTED] | -109% |
| Overall total | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | 100% |

Source: sheet 'Results' of the Economic Evaluation workbook. Adapted using the corrected dose of trastuzumab in each treatment arm. CT = computerised tomography, LVEF = left ventricular ejection fraction, mBC = metastatic breast cancer.

- 6.50 The results of key univariate sensitivity analyses are summarised in Table 18. Additional sensitivity analyses were conducted during the evaluation. The PSCR strongly disagreed on the appropriateness of presenting an ICER which omits the costs and outcomes in the metastatic breast cancer setting. The ESC considered that this was informative in terms of demonstrating the impact of the treatment of metastatic disease on the ICER.
- 6.51 The ICER was most sensitive to the estimated duration of treatment effect for PFS, duration of treatment for metastatic breast cancer, and the incremental costs and QALYs associated with the metastatic breast cancer health states. The ESC noted that the ICER was relatively robust to single parameters moving in reasonable ranges, however the ICER was highly sensitive to the inclusion of PFS benefit for the addition of pertuzumab which may not be reasonable.

Table 18: Sensitivity analyses

| Analyses | Incremental cost | Incremental QALY | ICER | % change to ICER |
|--|------------------|------------------|---------------|------------------|
| Base case (respecified) | \$ [REDACTED] | 0.588 | \$ [REDACTED] | 0% |
| Univariate analyses | | | | |
| PFS extrapolation (base case exponential extrapolation) | | | | |
| Weibull | \$ [REDACTED] | 0.63 | \$ [REDACTED] | -15% |
| Log-normal | \$ [REDACTED] | 0.661 | \$ [REDACTED] | -27% |
| Log-logistic | \$ [REDACTED] | 0.633 | \$ [REDACTED] | -17% |
| Duration of treatment effect (base case continues to Year 7, tapers to null at Year 10) | | | | |
| Tapers from 7 years to null at 15 years | \$ [REDACTED] | 0.595 | \$ [REDACTED] | -3% |
| Tapers from 5.1 years to null at 10 years | \$ [REDACTED] | 0.572 | \$ [REDACTED] | 7% |
| Null after trial period (5.1 years) | \$ [REDACTED] | 0.521 | \$ [REDACTED] | 31% |
| No treatment effect (PFS for Ptz+T+Chemo = PFS for T+Chemo) | \$ [REDACTED] | 0.126 | \$ [REDACTED] | 836% |
| Duration of treatment for mBC (base case from risk share arrangement) | | | | |
| Prescriptions per patient (DUSC analysis July 15 to Jun 16) ¹⁷ | \$ [REDACTED] | 0.588 | \$ [REDACTED] | 48% |
| Prescriptions per patient (DUSC analysis July 16 to June 17) ⁷ | \$ [REDACTED] | 0.588 | \$ [REDACTED] | 40% |
| Incremental costs for mBC (base case -\$ [REDACTED]) | | | | |
| No incremental costs for mBC | \$ [REDACTED] | 0.588 | \$ [REDACTED] | 116% |
| Multivariate analyses –incremental costs and QALYs for mBC (base case -\$ [REDACTED] and -0.149 QALY) | | | | |
| No incremental costs or QALYs for mBC | \$ [REDACTED] | 0.737 | \$ [REDACTED] | 72% |

Source: Table 3.23, p123 of the submission and economic evaluation workbook. Adapted using the corrected dose of trastuzumab in each treatment arm.

ICER = incremental cost effectiveness ratio, IPD = individual patient data, PFS = progression free survival, Ptz+T+Chemo = pertuzumab + trastuzumab + chemotherapy, QALY = quality adjusted life year, T+Chemo = trastuzumab + chemotherapy.

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

Drug cost/patient/course

6.52 Table 19 compares the drug cost per patient per course for Ptz+T+Chemo and T+Chemo in NEOSPHERE, the economic evaluation and financial estimates.

¹⁷ DUSC (February 2018) Medicines for the treatment of HER2 positive metastatic breast cancer: predicted versus actual analysis

Table 19: Drug cost per patient for proposed and comparator drugs

| | P+T Trial dose and duration | P+T Model | P+T Financial estimates | T Trial dose and duration | T Model | T Financial estimates |
|---|--|--|--|--|-----------------------|--------------------------------------|
| Mean dose | P: 2,060 mg ^a T: 6,431 mg ^a | P: 2,061 mg ^b T: 6,497 mg ^b | P: 2,100mg ^c T: excl. | 6,947 mg ^a | 6,764 mg ^b | Excl. |
| Mean duration | P: 3.9 cycles T: 15.6 cycles | n/a | P: 4 cycles T: excl. | 16.3 cycles | n/a | Excl. |
| Cost/patient/course | P: \$ [REDACTED] T: \$ [REDACTED] | P: \$ [REDACTED] T: \$ [REDACTED] | P: \$ [REDACTED] T: excl. | \$ [REDACTED] | \$ [REDACTED] | Excl. |
| Cost of neoadjuvant + adjuvant treatment | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | Excl. |

Source: Table 3.10, p 109 of the submission, sheets 'Drug Doses & Acquisition Costs' and 'Results' of the Economic Evaluation workbook, Table 29, p109 of NEOSPHERE CSR June 2011, Table 13, p60 of NEOSPHERE CSR March 2013. Adapted using corrected dose of trastuzumab in each treatment arm.

Excl. = excluded; n/a = not applicable; P+T = pertuzumab + trastuzumab; T = trastuzumab

^a mean total dose received, ^b prescribed dose per cycle multiplied by the proportion of patients remaining on treatment, ^c prescribed dose,

- 6.53 The cost per patient per course for pertuzumab based on the trial dose and duration was calculated during the evaluation assuming all patients received the initial dose of 840mg, then the continuing dose of 420mg for an average of 2.9 cycles. The cost per patient per course for trastuzumab in each arm was calculated by dividing the total mean dose by the mean duration to estimate an average dose, number of vials, and cost per cycle. The cost per cycle was multiplied by the mean number of cycles to estimate the cost per treatment course.
- 6.54 The submission modelled a total cost of \$ [REDACTED] per treatment course, comprising four cycles of neoadjuvant Ptz+T+Chemo therapy and 14 cycles of adjuvant T+Chemo therapy. This was incorrectly calculated using the average dose of trastuzumab (mean dose allowing for treatment discontinuation, divided by mean cycles) in the NEOSPHERE trial, multiplied by the proportion of patients remaining on treatment, which double-counted patients discontinuing treatment. The corrected modelled cost per treatment course of Ptz+T+Chemo is \$ [REDACTED]. This compares with \$ [REDACTED] for four cycles of neoadjuvant T+Chemo and 14 cycles of adjuvant T+Chemo. The PSCR acknowledged this error and agreed with the corrected values.
- 6.55 The financial estimates assumed all patients received the prescribed dose of pertuzumab for the full 4 cycles (initial dose of 840mg and three continuing doses of 420mg). This overestimated the cost of pertuzumab by less than \$10 million per patient. This translated to an overestimate of approximately less than \$10 million over six years.
- 6.56 The economic and financial models excluded the cost of chemotherapy in each arm. This is reasonable as the amount of chemotherapy administered in NEOSPHERE is approximately equal in each arm.
- 6.57 The financial estimates did not consider the cost of neoadjuvant/adjuvant trastuzumab. This was not appropriate. The economic model, which accounts for treatment discontinuation, indicated that the addition of pertuzumab results in decreased use and cost of trastuzumab in the neoadjuvant/adjuvant setting,

equivalent to less than \$10 million per patient. Applied to the financial estimates, this translated to an overestimate of approximately less than \$10 million over six years. The ESC also noted that the financial estimates did not include cost offsets associated with reduced utilisation of subsequent treatments, specifically for metastatic breast cancer. The ESC considered that this was inappropriate and is discussed further in the Financial Implications section.

Estimated PBS usage & financial implications

- 6.58 This submission was considered by DUSC.
- 6.59 The submission employed a modified market share approach. The HER2+ early breast cancer market size and growth was estimated using trastuzumab prescriptions from 2016 to 2018. The neoadjuvant market and uptake of pertuzumab in this setting were estimated using market research and clinical inputs. The DUSC considered this approach to be reasonable.
- 6.60 Table 20 outlines the key inputs in the financial estimates.

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Table 20: Key inputs for financial estimates

| Parameter | Value applied and source | Comment |
|---|--|--|
| Market size (year 0) | Initial scripts: 2,486. Trastuzumab utilisation data for 2016-2018 (3-weekly IV administration items) Continuing scripts: 7,458. Assumed three continuing scripts for each initial script | This is reasonable |
| Annual growth rate for eBC | 2.1%. Trastuzumab utilisation data for 2016-2018 (all trastuzumab eBC items excluding 4350R) | Item 4350R was used to calculate market size but omitted from growth calculations. Including 4350R reduces the annual growth rate to 1.75%. The pre-PBAC response accepted 1.75% annual eBC growth rate be applied to estimates, as suggested by DUSC. |
| Uptake rate – neoadjuvant treatment for eBC | 27% in Year 1. PBS 10% sample 42% in Year 2. Assumption 52% in Years 3+. Victorian Registry data and market research (METIS 2018) | This is consistent with PBAC advice provided for T-DM1 in eBC (para. 6.49, p29, PSD, November 2019 PBAC meeting) |
| Uptake rate – pertuzumab | 60% in Year 1. Patients self-funding in HER-START 70% in Year 2. Assumption 80% in Years 3+. Market research (METIS 2018) | This is reasonable, but the timing of market saturation is uncertain. Clinician advice indicates uptake may reach 80% sooner than Year 3. DUSC proposed the uptake rate in year 6 be 95%, the pre-PBAC response revised estimates based on uptake of 95% from year 4. |
| Cost of pertuzumab for eBC | \$3,072.37 (AEMP of pertuzumab 420mg vial, 1 Nov 2019) | As requested |
| Cost of trastuzumab for eBC | Excluded from financial estimates | The economic evaluation incorporates cost offsets associated with reduced utilisation of trastuzumab for eBC in the Ptz+T+Chemo arm. Revised in the pre-PBAC response. |
| Duration of pertuzumab treatment | All patients receive an initial dose of 840mg and three continuing doses of 420mg | This is inconsistent with the economic evaluation which incorporates the proportion of patients remaining on treatment |
| Offsets for subsequent treatment | A scenario analysis is presented that includes cost offsets for reduced utilisation of T-DM1 in eBC Cost offsets for pertuzumab, trastuzumab, and T-DM1 in mBC were not included | This is inconsistent with Section 3 which does not include T-DM1 in eBC and does include substantial cost offsets for pertuzumab, trastuzumab and T-DM1 in mBC. Cost offsets associated with downstream reduced use of pertuzumab, trastuzumab and T-DM1 were included in the pre-PBAC response. |
| MBS costs | Excluded from financial estimates | This is inconsistent with the economic model, which includes changes in MBS utilisation (e.g. intravenous drug administration). Revised in the pre-PBAC response. |

Source: Table 4.2, p130 of the submission, p128 of the submission, and sheet '2d. Scripts- market' of Utilisation and Cost Model workbook
eBC = early breast cancer, IV = intravenous, mBC = metastatic breast cancer, PBAC = pharmaceutical benefits advisory committee; PBS = pharmaceutical benefits schedule, Ptz+T+Chemo = pertuzumab + trastuzumab + chemotherapy, T-DM1 = trastuzumab emtansine.

6.61 Table 21 presents the estimated use and financial implications of listing pertuzumab. The submission did not include the costs of co-administered trastuzumab and chemotherapy. While excluding chemotherapy is reasonable, as the amount of chemotherapy administered in NEOSPHERE is approximately equal in each arm, the

cost of neoadjuvant and adjuvant treatment with trastuzumab was considered in the economic evaluation. Cost offsets associated with reduced utilisation of trastuzumab and T-DM1 and subsequent treatments specifically for metastatic breast cancer, were included in revised estimates presented in the pre-PBAC response (Table 21 below).

- 6.62 The submission stated that the addition of pertuzumab to neoadjuvant T+Chemo for early breast cancer would not result in additional MBS utilisation. This was inconsistent with the economic model which included changes in MBS utilisation, including intravenous drug administration, medical assessments, diagnostic imaging and blood tests. This was not addressed in the pre-PBAC response.

Table 21: Utilisation and Cost model for neoadjuvant pertuzumab listing revised in the pre-PBAC response

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|--------|--------|--------|--------|--------|--------|
| Estimated extent of use | | | | | | |
| Number of patients treated ^a | | | | | | |
| Number of scripts dispensed | | | | | | |
| Estimated financial implications of pertuzumab | | | | | | |
| Cost to PBS/RPBS less copayments | \$ | \$ | \$ | \$ | \$ | \$ |
| Estimated financial implications for other medicines | | | | | | |
| Trastuzumab (eBC) costs | -\$ | -\$ | -\$ | -\$ | -\$ | -\$ |
| T-DM1 (eBC) costs | -\$ | -\$ | -\$ | -\$ | -\$ | -\$ |
| mBC costs | \$ | \$ | \$ | \$ | \$ | \$ |
| Net financial implications | | | | | | |
| Net cost to PBS/RPBS | \$ | \$ | \$ | \$ | \$ | \$ |

Source: Pre-PBAC response p3, 'Trastuzumab savings', 'T-DM1 savings' and '5.Impact – Net' worksheets in the Utilisation and Cost model_ESC.xls

PBS = pharmaceutical benefits schedule; RPBS = repatriation pharmaceutical benefits schedule.

^a Annual growth rate revised to 1.75% as per DUSC advice; Uptake rate increased to 95% from year 4; Revised Net cost PBS/RPBS includes trastuzumab and adjuvant T-DM1 cost savings presented in the PSCR revised Utilisation and cost model; downstream mBC costs are incurred in the first two years of listing due to the increased rate of loco-regional recurrences observed in NEOSPHERE.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

- 6.63 The total cost to the PBS/RPBS of listing pertuzumab was estimated to be less than \$10 million in Year 6, and a total of \$60 – \$100 million in the first six years of listing in the revised estimates from the pre-PBAC response.
- 6.64 The submission presented a scenario analysis where use of Ptz+T+Chemo resulted in a 17% increase in pCR and corresponding decrease of T-DM1 use in the adjuvant setting. Based on T-DM1 financial estimates from the November 2019 PBAC meeting, a PBS listing for neoadjuvant pertuzumab would result in \$20 – \$30 million reduction in T-DM1 cost over six years. These cost offsets were not included in the economic model.

Quality Use of Medicines

- 6.65 The submission cited 11 ongoing studies for pertuzumab in early breast cancer, including one Australian study. The submission claimed these trials are not expected to affect the current registration status or PBS listing of pertuzumab, but will increase the knowledge and confidence of Australian prescribers.

Financial Management – Risk Sharing Arrangements

- 6.66 The submission sought PBS listing for up to six cycles of pertuzumab based on the TGA indication and results of the TRYPHAENA trial. The submission proposed a risk sharing arrangement (RSA) in the form of a pertuzumab expenditure cap, whereby the Sponsor would pay for any use of pertuzumab beyond four cycles of treatment. This was to address the uncertainty regarding the duration of treatment with pertuzumab. However, uncertainty regarding the annual growth rate of eBC and pertuzumab uptake are not addressed by the proposed arrangement. It is also not clear how this RSA would interact with the arrangement currently in place for pertuzumab plus trastuzumab in the metastatic setting.
- 6.67 DUSC noted the mean number of pertuzumab cycles in the NEOSPHERE trial was 3.7. DUSC commented that it is likely some patients will not finish four cycles of pertuzumab, and that an RSA may not rebate cycles five and six if some patients receive less than four cycles. DUSC considered the estimate of 4 cycles per patient was an overestimate and considered 3.7 would be a more reasonable estimate. The pre-PBAC response maintained that it was appropriate to assume 4 cycles, as patients in the NEOSPHERE trial could receive 4 cycles prior to surgery. The ESC questioned whether the number of cycles of pertuzumab reimbursed in the neoadjuvant setting should be in addition to or included with the cycles currently reimbursed in the metastatic setting.
- 6.68 The ESC noted that there are caps in place for T-DM1 and pertuzumab in the metastatic setting. The cost-effectiveness analysis assumed cost offsets for reduced use of T-DM1 and pertuzumab in the metastatic breast cancer setting due to fewer patients progressing to metastatic disease. To ensure the modelled cost-offsets are realised, the ESC considered that it may be appropriate to reduce the T-DM1 and pertuzumab expenditure caps in the metastatic breast cancer setting in line with the assumptions and outputs from the economic model for subsequent treatments.
- 6.69 As outlined in the 'economic analysis' section, the ESC considered that the impact of pertuzumab on reducing downstream use of T-DM1 in the adjuvant setting should be incorporated in the economic model. In line with this, the ESC considered that the cost-offsets from reduced use of T-DM1 may also need to be incorporated into any expenditure caps that may apply to T-DM1 in the adjuvant setting.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend pertuzumab, in combination with trastuzumab and chemotherapy, for the neoadjuvant treatment of HER-2+ locally advanced, inflammatory or early stage (≥ 2 cm in diameter or node positive) breast cancer. The PBAC considered that there was no evidence that neoadjuvant pertuzumab would improve patient outcomes if it were added to the current clinical algorithm which includes standard chemotherapy in the neoadjuvant setting and for patients who do not achieve a tpCR, trastuzumab emtansine (T-DM1) in the adjuvant setting. Given the uncertain clinical effectiveness, the PBAC considered that the cost-effectiveness of adding pertuzumab to current therapy was not able to be assessed.
- 7.2 The PBAC noted the nominated comparator for pertuzumab + trastuzumab + chemotherapy (P+T+Chemo) was trastuzumab + chemotherapy (T+Chemo). The PBAC recalled its previous advice that any future submissions for therapies for HER2+ eBC would need to account for the availability and efficacy of T-DM1 and demonstrate benefit in a treatment algorithm that includes T-DM1 (para 7.3, trastuzumab emtansine, Public Summary Document, November 2019). Consistent with this, the PBAC agreed with the ESC that the relevant comparison was sequential pertuzumab and T-DM1 (P+T+Chemo followed by T-DM1 in the adjuvant setting for patients without pCR) compared with T-DM1 (T+Chemo followed by T-DM1 in the adjuvant setting for patients without pCR).
- 7.3 The PBAC noted that the primary evidence included in the submission compared four cycles of pertuzumab, trastuzumab and docetaxel (Ptz+T+D; N=107) and T+D (N=107) as neoadjuvant treatment in a Phase II, open label, randomised trial in treatment-naïve women with HER2-positive breast cancer (NEOSPHERE). The PBAC noted that a Phase III double-blind study was identified during the evaluation which compared four cycles of Ptz+T+D (n=219) versus T+D (N=110) as neoadjuvant treatment in chemotherapy-naïve Asian women with HER2-positive breast cancer (PEONY).
- 7.4 The PBAC noted that the primary endpoint in NEOSPHERE was pathological complete response in the breast (bpCR) with total response (tpCR) assessed post-hoc. In PEONY the primary endpoint was tpCR. The PBAC considered tpCR to be more clinically relevant than bpCR. The PBAC noted, although meta-analyses of neoadjuvant trial data have indicated this outcome informs prognosis, that tpCR has not been definitively demonstrated to be a surrogate endpoint for disease free or overall survival.
- 7.5 The PBAC noted tpCR increased by approximately 18% with the addition of neoadjuvant pertuzumab in both NEOSPHERE (17.8%; 95% CI 4.6%, 31.0%, p=0.008) and PEONY (17.5%, 95% CI 6.9%, 28.0%, p=0.001). The PBAC noted this difference exceeded the minimal clinically important difference (MCID) defined in the submission of 15%. However, the PBAC considered the MCID of 15% was not adequately justified, noting the role of tpCR as a surrogate measure for patient relevant outcomes was

- unclear, especially with the availability of T-DM1 in the adjuvant setting for patients without a tpCR.
- 7.6 In addition to T-DM1 not being used in the adjuvant setting, the PBAC noted anthracycline-based regimens were not permitted in the neoadjuvant setting in NEOSPHERE or PEONY and were instead administered in the adjuvant setting. The PBAC noted that anthracyclines are a key component of neoadjuvant chemotherapy in clinical practice as they improve tpCR rates, and considered that the majority of Australian patients would receive an anthracycline before surgery. The PBAC noted that the tpCR with Ptz+T+D in NEOSPHERE and PEONY (approximately 39%) was similar to (and potentially lower than) rates achieved with anthracyclines in the neoadjuvant setting without pertuzumab (45-55% in Robidoux et al, 2013 and Buzdar et al, 2013), and considered it was unclear if neoadjuvant pertuzumab would increase tpCR when used with anthracycline+taxane based neoadjuvant chemotherapy.
- 7.7 The PBAC noted that there was no improvement in PFS or DFS demonstrated in the NEOSPHERE trial (PFS HR=0.69, 95% CI 0.34, 1.40; DFS HR=0.60, 95% CI 0.28, 1.27), and that the trial was not powered to assess these outcomes. The PBAC further noted that in the KATHERINE trial patients with residual disease derived a similar benefit from adjuvant T-DM1 regardless of whether they received pertuzumab in addition to trastuzumab in the neoadjuvant setting, and that the DFS at 3 years was high (88%) and similar to that observed with neoadjuvant pertuzumab (92% at 3 years). The PBAC considered that with the current treatment algorithm, it is unclear whether patients who achieve pCR post neoadjuvant therapy have improved DFS or OS over patients with residual disease who receive adjuvant T-DM1. The PBAC also considered it is unclear whether patients who do not achieve a pCR and go on to receive adjuvant T-DM1 derive any benefit from neoadjuvant pertuzumab.
- 7.8 The PBAC considered the claim of superior efficacy of Ptz+T+D compared with T+D (and hence the claim of superior efficacy of Ptz+T+Chemo vs T+Chemo) was not adequately supported because of: the limited applicability of the trials to current clinical practice (with anthracyclines used in the adjuvant rather than neoadjuvant setting, and T-DM1 not used in patients without a pCR); a difference in survival outcomes not being demonstrated; and the unknown impact of pCR on patient relevant outcomes, especially with the availability of T-DM1 for patients who do not achieve a pCR.
- 7.9 The PBAC considered the claim of non-inferior safety of Ptz+T+D compared with T+D was not adequately supported because of the significant increase in left ventricular systolic dysfunction in NEOSPHERE (8.4% vs 1.9% of patients) and the significant increase in diarrhoea (38.5% vs 16.4% of patients) and infusion-related reactions (22.0% vs 9.1%) in PEONY.
- 7.10 The PBAC considered it was not possible to assess the cost-effectiveness of adding pertuzumab in the neoadjuvant setting due to the unknown extent of clinical benefit. The PBAC further noted that the economic analysis was based on the PFS results from

NEOSPHERE which were not statistically significant and hence the modelled outcomes were highly uncertain.

- 7.11 The PBAC considered that, due to the unknown clinical benefit of pertuzumab in the neoadjuvant setting, its role in clinical practice was also unknown and hence it was not possible to assess the financial implications associated with the requested PBS listing of pertuzumab.
- 7.12 The PBAC considered that a resubmission would require additional clinical data in order to address the uncertainties associated with the clinical benefit, specifically:
- whether neoadjuvant pertuzumab increases tpCR when used with anthracycline+taxane based neoadjuvant chemotherapy; and
 - if there is an increase in the tpCR, whether this increase leads to improved PFS or DFS over the current treatment algorithm which includes adjuvant T-DM1
- 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 through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Roche is disappointed with the outcome and is committed to working with the PBAC to ensure that Australian patients with early breast cancer can access the optimal anti-HER2 neoadjuvant therapy.