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

1 Purpose of submission

1.1 The Standard Re-entry submission requested a Section 100 – Efficient Funding of Chemotherapy (EFC), Authority Required (Telephone/Electronic) listing for pertuzumab in combination with trastuzumab and chemotherapy (P+T+Chemo) as neoadjuvant treatment of patients with human epidermal growth factor receptor 2 (HER2) positive, locally advanced, inflammatory or early stage (>2 cm in diameter or node positive) early breast cancer (eBC). The resubmission referred to the target population as high risk eBC.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus trastuzumab in combination with chemotherapy (T+Chemo). Table 1 summarises the components of the overall clinical claim addressed by the resubmission.

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

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 (840 mg initially followed by 420 mg every 3 weeks) in combination with trastuzumab and chemotherapy (P+T+Chemo) for the neoadjuvant treatment of high risk eBC for up to 6 cycles.
Comparator	Trastuzumab in combination with chemotherapy (T+Chemo).
Outcomes[a]	Primary endpoint • pCR (total, breast) Secondary endpoints • Complete response • Survival (OS, PFS, DFS) • AEs
Clinical claim	Pertuzumab significantly improves the rates of pCR among patients with high risk eBC when added to trastuzumab and chemotherapy in the neoadjuvant setting and has an inferior, yet manageable, safety profile.[b]

Source: Table 1-1, p3 of the resubmission, pp27-28 of the resubmission. Underline indicates changes compared to the March 2020 submission.
AE=Adverse event; DFS=Disease-free survival; eBC=early breast cancer; H=trastuzumab; HER2=Human epidermal growth factor receptor 2; pCR=pathological complete response; OS=Overall survival; P=Pertuzumab; PFS=Progression-free survival; T=trastuzumab.
[a] Outcomes in the March 2020 submission were defined as Primary endpoint: pCR; Secondary Endpoints: OS, PFS, DFS, AEs".
[b] Table 1.1 of the March 2020 submission did not include a clinical claim for safety. The clinical claim presented in Section 2.8.2 of the March 2020 submission was "P+H+Chemo for the neoadjuvant treatment of high risk eBC is associated with superior comparative efficacy and non-inferior comparative safety to H+Chemo".

2 Background

Registration status

2.1 Pertuzumab was approved by the TGA on 20 May 2016 for the following indication:

- 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. [1]

2.2 Pertuzumab is also registered for the following additional indications that were not part of this PBAC resubmission:

- In combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence (4 August 2018). [2]

[1] Australian Public Assessment Report for pertuzumab. Australian Government, Dept of Health. Therapeutic Goods Administration. https://www.tga.gov.au/sites/default/files/auspar-pertuzumab-160616.pdf [accessed 11-Dec-24]
[2] PERJETA (Roche Products Pty Ltd). Australian Government. Therapeutic Goods Administration. https://www.tga.gov.au/resources/prescription-medicines-registrations/perjeta-roche-products-pty-ltd [accessed 11-Dec-24]

- 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 (6 May 2013). [3]

Previous PBAC consideration

2.3 Pertuzumab was previously considered by the PBAC for neoadjuvant treatment of high risk eBC at the March 2020 PBAC meeting. Table 2 summarises the key matters of concern at the March 2020 PBAC meeting and how the resubmission addressed them.

2.4 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] PERJETA pertuzumab (rch) 30mg/mL concentrate injection vial (196218). Australian Government. Therapeutic Goods Administration. https://www.tga.gov.au/resources/artg/196218 [accessed 11-Dec-24]

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Clinical management algorithm	The clinical management algorithm should consider anthracyclines as neoadjuvant treatment and T-DM1 as adjuvant treatment (paras. 4.4, 5.2, 7.2. 7.6, March 2020 PSD)	Addressed. Clinical management algorithm considered neoadjuvant anthracyclines and adjuvant T-DM1.
Effectiveness of P+T+Chemo including anthracyclines	No evidence of the effectiveness of neoadjuvant pertuzumab when used with anthracyclines was presented (paras. 6.12, 6.13, 7.6, 7.8, 7.12, March 2020 PSD)	Addressed. Second literature search identified 14 studies where P+T+Chemo included anthracyclines as part of the chemotherapy regimen.
Effectiveness of sequential treatment with neoadjuvant P+T+Chemo and adjuvant T-DM1	No evidence of the effectiveness of neoadjuvant pertuzumab followed by adjuvant T-DM1 was presented (paras. 6.28, 7.1, 7.7, 7.8, 7.12, March 2020 PSD)	Partially addressed. A study by Swain (2022) identified that translated pCR into a HR for EFS, which was compared to the iDFS HR for T-DM1 in the KATHERINE trial. There were transitivity issues between the trials included in the comparison. The ESC agreed this was partially addressed but noted that there were no studies that directly assessed the effectiveness of neoadjuvant pertuzumab followed by adjuvant T-DM1.
Clinical effectiveness – PFS	There was no improvement in PFS or DFS demonstrated in the NEOSPHERE trial, and the trial was not powered to assess these outcomes (paras. 6.28, 7.7, March 2020 PSD)	Not addressed. Survival outcomes remained non-significant in the included trials and were not primary outcomes.
Clinical effectiveness - pCR	The ESC noted that the PBAC framework for assessing a proposed surrogate measure was not addressed. The PBAC noted that tpCR has not been demonstrated to be a surrogate endpoint for DFS or OS (paras. 6.20, 7.4, March 2020 PSD)	Addressed. Additional evidence was presented in the submission and PSCR.
Safety – cardiac events, diarrhoea, and infusion-related reactions	The PBAC considered the claim of non-inferior safety was not adequately supported given the increase in left ventricular systolic function, diarrhoea, and infusion-related reactions (para. 7.9, March 2020 PSD)	Addressed. The clinical claim for safety was revised to 'inferior safety'. Additional safety data were provided with the resubmission.
Economic model structure	The economic model structure did not reflect the breast cancer treatment algorithm because it did not consider adjuvant treatment with T-DM1 (paras. 6.32, 6.33, March 2020 PSD)	Addressed. The economic model structure in the resubmission was based on the economic model for T-DM1 considered by the PBAC in November 2019. A neoadjuvant decision tree was added to the T-DM1 Markov structure and an additional Markov trace was added to reflect survival following pCR (HR from Swain 2022).
Economic model relied on immature PFS data	The economic model was based on PFS data from NEOSPHERE which were immature and highly uncertain (paras. 6.40 and 7.10, March 2020 PSD)	Addressed. The economic model in the resubmission used pCR from studies of P+T+Chemo (including anthracyclines) and iDFS data from theT-DM1 KATHERINE trial and Swain 2022. However, the new model relied on the surrogate relationship between pCR and EFS.
Downstream costs in the financial estimates	The financial estimates did not include downstream cost offsets from changes to adjuvant and metastatic treatments (para. 6.57, March 2020 PSD)	Addressed. The financial estimates included downstream cost offsets for adjuvant and subsequent treatments.

Source: Table 1-4, pp9-17 of the resubmission; pertuzumab, PSD, March 2020 PBAC meeting.

DFS = disease free survival; EFS=event free survival; iDFS=invasive disease free survival; HR=hazard ratio; OS = overall survival; PBAC=Pharmaceutical Benefits Advisory Committee; pCR=pathological complete response; PSD=public summary document; P+T+Chemo=pertuzumab + trastuzumab + chemotherapy; T-DM1=trastuzumab emtansine.

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

3 Requested listing

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount (vials)	№. of Rpts
Chemotherapy items for public hospital use			
PERTUZUMAB – initial Solution for IV infusion	$5,927.63 published price $[redacted] effective price	2	0
PERTUZUMAB – continuing Solution for IV infusion	$3,008.88 published price $[redacted] effective price	1	4
Chemotherapy items for private hospital use			
PERTUZUMAB – initial Solution for IV infusion	$6,054.02 published price $[redacted] effective price	2	0
PERTUZUMAB – continuing Solution for IV infusion	$3,094.41 published price $[redacted] effective price	1	4
Available brands			
Perjeta (pertuzumab 420 mg/14 mL solution for IV infusion, 1 vial)			
Category / Program: Section 100 – Efficient Funding of Chemotherapy			
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐			
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)			
Indication: HER2 positive early breast cancer			
Treatment Phase: Initial treatment – neoadjuvant treatment			
Clinical criteria:			
Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by in situ hybridisation (ISH)			
AND			
Clinical criteria:			
Patient must have locally advanced, inflammatory or early stage (tumour >2 cm in diameter or lymph node positive) breast cancer,			
AND			
Clinical criteria:			
Patient must not have undergone surgery for this condition,			
AND			
Clinical criteria:			
The treatment must be in combination with trastuzumab,			
AND			
Clinical criteria:			
The treatment must be in combination with chemotherapy,			
AND			
Clinical criteria:			
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			

Clinical criteria:
Patient must not receive more than 1 treatment cycle under this restriction.
Prescribing Instructions: Details (date, unique identifying number/code, or provider number) of the pathology report from an Approved Pathology Authority confirming evidence of HER2 gene amplification by in situ hybridisation (ISH) must be provided at the time of application. The pathology report must be documented in the patient's medical records. Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval. Treatment with this drug for this condition must not exceed 6 treatment cycles (18 weeks) of combined initial and continuing treatment

Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
Indication: HER2-positive early breast cancer
Treatment Phase: Continuing treatment – neoadjuvant treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition,
AND
Clinical criteria:
The treatment must be in combination with trastuzumab,
Clinical criteria:
The treatment must be in combination with chemotherapy,
AND
Clinical criteria:
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
Clinical criteria:
Patient must not receive more than 5 treatment cycles under this restriction.
Prescribing Instructions: Treatment with this drug for this condition must not exceed 6 treatment cycles (18 weeks) of combined initial and continuing treatment.

3.1 The requested effective price (AEMP = $[redacted]) was lower than the requested price in the March 2020 submission (AEMP = $[redacted]). The resubmission stated that this represented a [redacted]% reduction in the price per vial compared to the previous submission.

3.2 The requested effective price was lower than the price of pertuzumab as treatment (in combination with trastuzumab and docetaxel) for metastatic breast cancer (mBC) (AEMP = $[redacted]).[4]

[4] Ex-manufacturer prices (Efficient Funding of Chemotherapy) – 1 December 2024. Available online at https://www.pbs.gov.au/info/industry/pricing/ex-manufacturer-price. [Accessed 16-Dec-24].

3.3 The resubmission noted the following discrepancies between the proposed PBS restrictions and the TGA PI and/or clinical trial evidence:

- The proposed threshold for left ventricular ejection fraction (LVEF) of ≥45% was misaligned with the pivotal clinical evidence and the TGA Product Information (PI) of ≥55%. The ESC previously accepted that it would be appropriate to align the LVEF criteria with the current trastuzumab listing (i.e., ≥45%) to allow patients to be eligible for both drugs if they are to be used concurrently (para. 3.4, pertuzumab, PSD, March 2020 PBAC meeting).
- In the pivotal clinical trials, participants were treated with neoadjuvant pertuzumab for either 4 (NEOSPHERE, PEONY, I-SPY2) or 6 (TRYPHAENA) cycles. The proposed restriction included up to 6 cycles of treatment, consistent with the TGA PI and treatment guidelines.
- The chemotherapy agents used in combination with pertuzumab in the pivotal clinical trials included docetaxel (NEOSPHERE, PEONY) and either an anthracycline regimen or carboplatin (TRYPHAENA). As per the original submission, the resubmission proposed that the restriction does not specify the chemotherapy agent or regimen to be used in combination with pertuzumab and trastuzumab. The ESC and DUSC previously considered it reasonable to not specify the chemotherapy regimen in the restriction (para. 3.4, pertuzumab, PSD, March 2020 PBAC meeting).

3.4 The requested listing included patients with inflammatory breast cancer, however there were only a small number of these participants included in the trials (17 in the NEOSPHERE trial, 9 in the TRYPHAENA trial, 0 in the PEONY trial, and the number was not reported for the I-SPY2 trial). The PBAC considered it was reasonable for the restrictions not to exclude these patients.

3.5 The PBAC agreed with the ESC it may be helpful to include “high risk” in the clinical criteria, for clarity: “Patient must have locally advanced, inflammatory or early stage high risk (tumour >2 cm in diameter or lymph node positive) breast cancer”.

3.6 The PBAC noted that the clinical place and cost effectiveness for pertuzumab were most established in the neoadjuvant setting, but considered that it would be preferable for the restrictions to allow treatment in the adjuvant setting (with or without prior neoadjuvant pertuzumab), to address equity issues, and consistent with the Australian PI and international guidelines.

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

4 Population and disease

4.1 Breast cancer is a complex condition made up of different subtypes, including HER2 positive. HER2 positive eBC occurs when breast cells overexpress the HER2 receptor

due to an oncogenic mutation in the HER2 gene; reported in 15-20% of all breast cancers.[5] HER2-positive tumours tend to be more aggressive than HER2-negative tumours and are associated with a less favourable prognosis.

4.2 The primary surgical goals of neoadjuvant systemic therapy are to achieve tumour or nodal downstaging, improve tumour resectability and decrease surgical morbidity and the extent of surgery. Neoadjuvant systemic therapy increases the feasibility of breast-conserving surgery among patients with Stage II-III breast cancer who would otherwise require a mastectomy. In patients with significant nodal disease, neoadjuvant systemic therapy can downstage axillary nodes, decrease the morbidity and extent of axillary surgery and render inoperable tumours as operable. In addition, patients with HER2-positive breast cancer are more likely to obtain a pCR and avoid axillary lymph node dissection after neoadjuvant therapy. Thus, these patients are likely to avoid complications associated with axillary lymph node dissection, such as lymphoedema. In patients with HER2-positive tumours, additional benefits of neoadjuvant systemic therapy include the potential to individualise adjuvant therapy options based on pathological response and to provide information about tumour status in vivo, allowing for escalation or de-escalation of therapy, as guided by response biomarkers.

4.3 The PBAC previously considered this population in the March 2020 submission for pertuzumab in the neoadjuvant setting and the July 2012 submission for trastuzumab to extend the existing trastuzumab listings to include neoadjuvant treatment for eBC and locally advanced breast cancer (para. 1.1, pertuzumab PSD, March 2020 PBAC meeting; Section 1, trastuzumab PSD, July 2012 PBAC meeting). The proposed patient population was unchanged from the March 2020 submission.

4.4 Pertuzumab is a recombinant, humanised monoclonal antibody which specifically targets the extracellular dimerisation domain (subdomain II) of the HER2 receptor. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity.

4.5 The resubmission stated that guidelines unanimously recommend neoadjuvant chemotherapy plus trastuzumab with or without pertuzumab for HER2 positive high risk eBC patients. The resubmission noted that the most recent guidance recommended neoadjuvant chemotherapy combined with dual HER2 blockade (i.e., pertuzumab and trastuzumab) as the preferred regimen.[6] The ESC noted that ESMO guidelines recommend 6-8 cycles of neoadjuvant P+T+Chemo.

4.6 The resubmission stated that there was inequity of access to neoadjuvant pertuzumab for patients with high risk eBC in Australia. In the absence of PBS funding, nearly half of eligible eBC patients are receiving access to neoadjuvant pertuzumab by patient

[5] Dowling GP, Keelan S, Toomey S, et al. 2023. Review of the status of neoadjuvant therapy in HER2-positive breast cancer. Front Oncol 13: 1066007.

[6] Loibl S, Andre F, et al. (2024) Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 35(2):159-182.

self-funding or via a hospital purchasing program. The PBAC noted that some patients are also self-funding pertuzumab in the adjuvant setting.

4.7 Following neoadjuvant treatment, patients receive surgery. Patients are then eligible for adjuvant treatment with trastuzumab emtansine (T-DM1) or trastuzumab. Patients with pathological complete response (pCR) receive adjuvant treatment with trastuzumab, while patients without pCR receive T-DM1. The Australian PI for pertuzumab recommends patients who start P+T+Chemo in the neoadjuvant setting should continue to receive adjuvant P+T to complete one year of treatment, and international guidelines include adjuvant pertuzumab as a treatment option for lymph node positive patients who have pCR following surgery, as well as for patients who do not undergo neoadjuvant treatment with pertuzumab but are considered high risk following surgery[7].

5 Comparator

5.1 The resubmission nominated T+Chemo as the main comparator. This was unchanged from the March 2020 submission. The intervention and comparator both included chemotherapy, which can involve a range of medicines.

5.2 The resubmission noted previous PBAC advice that the relevant comparison for P+T+Chemo should take into account sequential pertuzumab and T-DM1, given the availability of T-DM1 as adjuvant therapy for patients with residual disease following treatment with trastuzumab plus taxane-based chemotherapy in the neoadjuvant setting. The resubmission maintained that T+Chemo was the appropriate comparator in the neoadjuvant setting; however, the clinical implications and cost-effectiveness, and financial of sequential use of T-DM1 in patients without a pCR were considered in the resubmission. The ESC considered this was reasonable.

5.3 The utilisation of trastuzumab for locoregional recurrence, and pertuzumab, T-DM1, and trastuzumab deruxtecan (T-DXd) in the metastatic setting could also be affected. This was not captured in the clinical trials but was considered in the economic analysis and financial estimates.

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.

[7] Harbeck N. Neoadjuvant and adjuvant treatment of patients with HER2-positive early breast cancer. Breast. 2022 Mar;62 Suppl 1(Suppl 1):S12-S16. doi: 10.1016/j.breast.2022.01.006. Epub 2022 Jan 19. PMID: 35148934; PMCID: PMC9097807.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (3) and organisations (5) via the Consumer Comments facility on the PBS website. The comments from health care professionals described equity of access issues, noting that many patients are currently self-funding pertuzumab. The comments also stated the inclusion of pertuzumab to the neoadjuvant regimen significantly increases the rate of pCR, which correlates with improved survival, reduces the extent of surgery, increases the chances of successful breast-conserving surgery, and helps identify patients with residual disease who may benefit from tailored post-surgical therapies. Input noted that the main side effects (diarrhea and reversible cardiomyopathy) can be easily managed and can reduce the need for other toxic treatments in the longer term.

6.3 The PBAC noted the advice received from Breast Surgeons ANZ who also noted that pCR is a valuable surrogate for survival endpoints and commented on the reduction in the extent of surgery and impacts on cosmetic outcomes and quality of life, citing several publications demonstrating the increase in breast conserving surgery associated with neoadjuvant pertuzumab. The PBAC noted that Breast Cancer Network Australia (BCNA) expressed strong support for PBS listing of pertuzumab. In addition to improved pCR rates BCNA noted the APHINITY trial (in the adjuvant setting) showed adding pertuzumab to the standard treatment of trastuzumab and chemotherapy significantly improves invasive disease-free survival (IDFS), especially for those with node-positive or hormone receptor-negative disease. Breast Surgeons ANZ, BCNA and Breast Cancer Trials noted that the addition of pertuzumab is recommended internationally and considered standard of care. Breast Cancer Trials noted that not being able to provide pertuzumab as standard of care prevents access for Australians to trials, and to the benefits of those trials. Breast Surgeons ANZ and BCNA also raised equity of access issues for pertuzumab. Rare Cancers Australia noted its support of PBS listing pertuzumab.

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 "highest priority for PBS listing" on the basis of the NEOSHPERE trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pertuzumab, which was limited to grade C (where A and B represent the grades with substantial improvement in survival outcomes)[8].

Clinical trials and studies

6.5 The resubmission was based on 3 head-to-head randomised controlled trials (RCTs) comparing P+T+Chemo to T+Chemo as neoadjuvant treatment for eBC:

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

- The NEOSPHERE trial had 4 arms that compared 4 cycles of P+T+Chemo (docetaxel) with 4 cycles of T+Chemo (docetaxel), 4 cycles of P+Chemo (docetaxel), and 4 cycles of T+Chemo (docetaxel) [N=417, n relevant to this resubmission = 214].
- The PEONY trial had 2 arms that compared 4 cycles of P+T+Chemo (docetaxel) with 4 cycles of T+Chemo (docetaxel) [N=328].
- The I-SPY2 trial is an ongoing adaptively randomised platform trial that evaluates multiple investigation agents in parallel against a common control within specific breast cancer subtypes. There were 3 arms relevant to HER2 positive participants: P+T+Chemo, P+T-DM1+Chemo, and T+Chemo. The chemotherapy backbone was paclitaxel with 4 cycles of HER2 targeted treatment (P+T, P+T-DM1, or trastuzumab) followed by 4 cycles of anthracycline treatment [relevant n = 76].

6.6 The resubmission also presented one supplementary RCT comparing 3 different chemotherapy regimens for P+T+Chemo as neoadjuvant treatment for eBC:

- The TRYPHAENA trial had 3 arms that compared P+T+Chemo with different chemotherapy backbones ([6 cycles P+T with 3 cycles 5-fluorouracil [5FU] + epirubicin + cyclophosphamide followed by 3 cycles docetaxel], [6 cycles P+T with 6 cycles docetaxel + carboplatin], [3 cycles 5FU + epirubicin + cyclophosphamide followed by 3 cycles P+T with 3 cycles docetaxel]) [N=225, relevant n=150].

6.7 The TRYPHAENA trial was excluded from the search for RCTs because it did not include comparative evidence for P+T+Chemo vs T+Chemo. However, it was included in the resubmission because it provided information on 6 neoadjuvant cycles, and assessed anthracycline-based or carboplatin-based neoadjuvant chemotherapy regimens, which were applicable in the Australian setting.

6.8 Additionally, the resubmission identified 14 observational studies comparing P+T+Chemo to T+Chemo where the neoadjuvant chemotherapy backbone included anthracyclines:

- Acevedo (2023) a retrospective population-cohort study from a breast cancer registry in Chile [N=372].
- HER2PATH (Bilici 2023) a retrospective, multicentre nationwide cohort study in Turkey [N=1,528].
- NeoPowER (Canino 2024) a retrospective, observational, multicentre review of medical records in Italy [N=260].
- Chang (2020) a retrospective database review from a tertiary hospital in Hong Kong [N=142].
- Cheng (2022) a retrospective multicentre study across 30 hospitals in China [N=1,032].

- Díaz-Redondo (2019) a retrospective review of clinical records in Spain [N=254].
- Neopearl (Fabbri 2023) a retrospective multicentre observational study in Italy [N=271].
- Hung (2022) a retrospective single centre cohort study in Taiwan [N=147].
- Jiao (2024) a retrospective multicentre cohort study in China [N=2,010].
- Little (2020) a retrospective case note study in the UK [N=176].
- Spring (2018) a retrospective review of electronic records in the US [N=121].
- Van der Voort (2022) a nationwide cohort analysis of national cancer registry data in the Netherlands [N=1,124].
- Vieira (2023) a retrospective review of electronic medical reports at a single site in Portugal [N=94].
- NBRST (Whitworth 2022) a prospective multicentre observational study in the US [N=295].

6.9 Finally, the resubmission presented Swain (2022) as part of its assessment of pCR as a surrogate measure for prevention of disease recurrence. Swain (2022) was a review that analysed the relationship between neoadjuvant pCR and event free survival (EFS) across 5 RCTs in participants who received pertuzumab, trastuzumab or both in the neoadjuvant and adjuvant settings. The 5 RCTs included in Swain (2022) were the NEOSPHERE, TRYPHAENA, BERENICE, HannaH, and KRISTINE trials.

6.10 The PBAC previously considered the NEOSPHERE, PEONY, and TRYPHAENA trials as part of the March 2020 submission. The I-SPY2 trial was unpublished at the time of the March 2020 PBAC submission. The PBAC has not previously considered the 14 observational studies including neoadjuvant anthracyclines or Swain (2022).

6.11 Details of the trials presented in the resubmission are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
RCTs: P+T+Chemo vs T+Chemo		
NEOSPHERE NCT00545688	A randomised, multicentre, 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. Gianni L, Pienkowski T, Im YH 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. Gianni L, Pienkowski T, Im YH 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. Gianni L, Pienkowski T, Im YH et al. Abstract S3-2: neoadjuvant Pertuzumab (P) and Trastuzumab (H): antitumor and Safety Analysis of a Randomized Phase II Study ('NeoSphere'). Gianni L, Pienkowski T, Im YH et al. Addition of pertuzumab (P) to trastuzumab (H)-based neoadjuvant chemotherapy significantly improves pathological complete response in women with HER2-positive early breast cancer: Result of a randomised phase II study (NEOSPHERE). Gianni L, Pienkowski T, Im YH et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P).	CSRs dated June 2011, March 2013, February 2014, and February 2015. *The Lancet Oncology* 2012; 13(1): 25-32. *The Lancet Oncology* 2016; 17(6): 791-800. *Cancer Res* 2010; 70 (24_Supplement): S3-2. *Breast* 2011; 20: S73. *Journal of Clinical Oncology* 2015; 33(15): suppl.505.
PEONY NCT02586025	A randomized, multicenter, double-blind, placebo-controlled, phase III study to evaluate pertuzumab in combination with docetaxel and trastuzumab as neoadjuvant 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. Huang L, Pang D, Yang H et al. Neoadjuvant-adjuvant pertuzumab in HER2-positive early breast cancer: final analysis of the randomized phase III PEONY trial. Shao Z, Pang D, Yang H 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. Duan C, Pang D, Yang H et al. Peony exploratory analyses of biomarker changes: From baseline to surgical samples in patients with HER2+ breast cancer. Shao Z, Pang D, Yang H et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive early or locally advanced breast cancer in the neoadjuvant setting: Efficacy and safety analysis of a randomized phase III study in Asian patients (PEONY). Shao Z, Pang D, Yang H et al. Final analysis of the Phase III PEONY trial: long-term efficacy and safety of neoadjuvant-adjuvant pertuzumab or placebo, plus trastuzumab and docetaxel, in patients with HER2- positive early or locally advanced breast cancer	CSRs dated June 2018, August 2022. *Nature Communications* 2014; 15(1): 2153. *JAMA Oncology* 2020; 6(3): e193692. *Journal of Clinical Oncology* 2024; 42(16):e15136. *Cancer Research* 2019; 79(4_supplement): P6-17-17. *Cancer Research* 2023; 83(5_supplement): PD18-03.

Trial ID	Protocol title/ Publication title	Publication citation
I-SPY2 NCT01042379	Clark AS, Yau C, Wolf DM et al. Neoadjuvant T-DM1/pertuzumab and paclitaxel/trastuzumab/pertuzumab for HER2+ breast cancer in the adaptively randomized I-SPY2 trial. Buxton M, DeMichele AM, Chia S et al. Efficacy of pertuzumab/ trastuzumab/ paclitaxel over standard trastuzumab/ paclitaxel therapy for HER2+ breast cancer: Results from the neoadjuvant I-SPY 2 TRIAL. Yee D, Demichele A, Isaacs C et al. Pathological complete response predicts event-free and distant disease-free survival in the I-SPY2 TRIAL.	*Nature communications* 2021; 12(1): 6428. *Cancer Research* 2016; 76(14_supplement): CT106. *Cancer Research* 2018; 78(4).
Supplementary RCT: P+T+Chemo vs P+T+Chemo		
TRYPHAENA NCT00976989	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. 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) 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.	CSRs dated May 2021, Dec 2012, Jan 2014, Sep 2016. *Annals of Oncology* 2013; 24(9): 2278-2284. *European Journal of Cancer* 2018; 89:27-35.
Pooled analysis		
Swain (2022)	Swain 2m, Macharia H, Cortes J et al. Event-Free Survival in Patients with Early HER2-Positive Breast Cancer with a Pathological Complete Response after HER2-Targeted Therapy: A Pooled Analysis	*Cancers* 2022; 14:5051
Studies: P+T+Chemo vs T+Chemo, neoadjuvant chemotherapy must include an anthracycline		
Acevedo (2023)	Acevedo F, Walbaum B, Medina L et al. The real-world outcome of human epidermal growth factor type-2 positive breast cancer patients receiving neoadjuvant therapy with or without pertuzumab.	*Cancer Res* 2023; 85(5_Supplement): P1-11-17.
HER2PATH	Bilici A, Olmez OF, Kaplan MA et al. Impact of adding pertuzumab to trastuzumab plus chemotherapy in neoadjuvant treatment of HER2 positive breast cancer patients: a multicenter real life HER2PATH study.	*Acta Oncologica* 2023; 62(4):381-390.
NeoPowER	Canino F, Barbolini M, De Giorgi U et al. Safety and efficacy analysis of neoadjuvant pertuzumab, trastuzumab and standard chemotherapy for HER2–positive early breast cancer: real–world data from NeoPowER study.	*BMC Cancer* 2024; 24:735.
Chang (2020)	Chang Y-K, Co M, Kwong A. Conversion rate from mastectomy to breast conservation after neoadjuvant dual target therapy for HER2-positive breast cancer in the Asian population.	*Breast Cancer* 2020; 27:456-463.
Cheng (2022)	Cheng Y, Xiang H, Xin L et al. Neoadjuvant therapy for early human epidermal growth factor receptor 2 positive breast cancer in China: A multicenter real-world study (CSBrS-015).	*Chinese Medical Journal* 2022; 135(19):2311-2318.
Díaz-Redondo (2019)	Díaz-Redondo T, Lavado-Valenzuela R, Jiminez B et al. Different Pathological Complete Response Rates According to PAM50 Subtype in HER2+ Breast Cancer Patients Treated With Neoadjuvant Pertuzumab/Trastuzumab vs. Trastuzumab Plus Standard Chemotherapy: An Analysis of Real-World Data.	*Frontiers in Oncology* 2019; 9:1178.

Trial ID	Protocol title/ Publication title	Publication citation
Neopearl	Fabbri A, Nelli F, Botticelli A et al. Pathologic response and survival after neoadjuvant chemotherapy with or without pertuzumab in patients with HER2-positive breast cancer: the Neopearl nationwide collaborative study.	*Frontiers in Oncology* 2023; 13:1177681.
Hung (2022)	Hung C-C, Tsai I-C, Hsu C-Y et al. Clinical Outcomes of Neoadjuvant Therapy in Human Epidermal Growth Factor Receptor 2 Breast Cancer Patients: A Single-Center Retrospective Study.	*J. Clin. Med.* 2022; 11:1434
Jiao (2024)	Jiao D, Li G, Dai H et al. Comparison of the Response to Neoadjuvant Therapy Between Immunohistochemistry HER2 (3+) and HER2 (2+)/ISH+ Early-Stage Breast Cancer: A Retrospective Multicenter Cohort Study.	*The Oncologist* 2024; 29:e877-e886.
Little (2020)	Little J, Forner S, Sim V et al. The differential impact of non-anthracycline treatment regimens on pathological complete response (pCR) rates by ER status after neoadjuvant single or dual HER2 targeted therapy (NACT): A single centre experience.	*Cancer Res* 2020; 80(4_Supplement): P2-16-31.
Spring (2018)	Spring L, Niemierko A, Haddad S et al. Effectiveness and tolerability of neoadjuvant pertuzumab containing regimens for HER2-positive localized breast cancer.	*Breast Cancer Res Treat.* 2018; 172(3):733-740.
Van der Voort (2022)	Van der Voort A, Liefaard MC, van Ramshorst MS et al. Efficacy of neoadjuvant treatment with or without pertuzumab in patients with stage II and III HER2-positive breast cancer: a nationwide cohort analysis of pathologic response and 5-year survival.	*The Breast* 2022; 110-115
Vieira (2023)	Vieira C, Borges A, Pereira FF et al. Pertuzumab in Combination with Trastuzumab and Docetaxel in the Neoadjuvant Treatment for HER2-Positive Breast Cancer.	*J Immunother Precis Oncol.* 2023l 6(1):1-9
NBRST (Whitworth 2022)	Whitworth PW, Bietsch PD, Murray MK et al. Genomic Classification of HER2-Positive Patients with 80-Gene and 70-Gene Signatures Identified Diversity in Clinical Outcomes With HER2-Targeted Neoadjuvant Therapy.	*JCO Percis Oncol* 2022; 6:e2200197.

Source: Tables 2-3 &2-54, pp39-43 & 122-126 of the resubmission; Appendix and References of the resubmission; Table 2.4, p37 of the March 2020 submission.
CSR=Clinical Study Report; P+T+Chemo=pertuzumab + trastuzumab + chemotherapy; T+Chemo=trastuzumab + chemotherapy.

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

Table 4: Key features of the included trials and studies

Trial	N[a]	Design / follow-up duration (years)	Chemo component (relevant arms)	Bias	Patient population	Key Outcomes
P+T+Chemo vs T+Chemo (RCTs) [b]						
NEOSPHERE	214	R, OL, MC; 5 yrs	4 x docetaxel cycles	Mod.	Chemotherapy-naïve participants with locally advanced, inflammatory or early stage (tumour >2 cm) HER2-positive BC.	Primary: bpCR Secondary: response, time to response, PFS, DFS, Safety Post-hoc: tpCR
PEONY	328	R, DB, MC; 5-yrs	4 x docetaxel cycles	Low	Chemotherapy-naïve participants with early stage (tumours >2 cm) or locally advanced HER2-positive BC.	Primary: tpCR Secondary: bpCR, response, EFS, DFS, OS, Safety
I-SPY2	76	R, OL, MC, AR; 4 yrs	12 weeks paclitaxel then 4 anthracycline cycles	Mod.	Adult women with HER2+ stage II or III breast cancer with primary tumours ≥ 2.5 cm clinically or ≥ 2.0 cm by imaging who have not received prior treatment for their BC.	Primary: tpCR Secondary: residual disease burden, EFS, DRFS, Safety
P+T+Chemo, different chemotherapy types (RCT) [b]						
TRYPHAENA	150	R, OL, MC; 5yrs	3+3: 3 x (5FU + epirubicin + cyclophospham-ide) cycles then 3 x docetaxel cycles 6: 6 x (docetaxel + carboplatin) cycles	Mod.	Chemotherapy-naïve participants with HER2-positive BC which was early stage, and >2 cm in diameter, or locally advanced or inflammatory.	Primary: Tolerability Secondary: bpCR, tpCR, response, time to response, PFS, DFS, OS
P+T+Chemo vs T+Chemo (all studies, chemo must include anthracyclines)						
Acevedo (2023)	372	Retro, cohort, registry	85.2% AC + taxane, 10.0% taxane only, 4.8% AC only.	Critical	Females with Stage I-III HER2 positive BC.	tpCR, DDFS
HER2PATH (Bilici 2023)	1,528	Retro, cohort, MC	P+T+Chemo: 83% received AC T+Chemo: 78.5% received AC	Critical	Female participants ≥18 years with histologically confirmed HER2+ BC.	tpCR, EFS, safety
NeoPowER (Canino 2024)	260	Retro, chart review, MC	P+T+Chemo: 44.4% AC, 0% 5-FU T+Chemo: 82.8% AC, 44% 5-FU	Serious	Participants ≥18 years, ECOG of 0 or 1; with operable, locally advanced or inflammatory BC (Stage II-III); HER2 overexpression confirmed by IHC or ISH.	tpCR, DRFS, OS, safety

Trial	N[a]	Design / follow-up duration (years)	Chemo component (relevant arms)	Bias	Patient population	Key Outcomes
Chang (2020)	142	Retro, chart review	3.5% AC + taxane, 1.4% FEC, 52.1% taxane only, 38.7% AC only, 1.4% carboplatin	Critical	Participants with non-metastatic, HER2-positive, non-inflammatory BC.	bpCR, tpCR
Cheng (2022)	1,032	Retro, MC	P+T+Chemo: 13.8% taxane only, 57% taxane + carboplatin, 29.3% taxane + AC + cyclophosphamide T+Chemo: 4.7% taxane only, 57.8% taxane + carboplatin, 34.1% taxane + AC + cyclophosphamide, 3.4% taxane + cyclophosphamide	Critical	Participants with early Stage I-III HER2-positive invasive female BC.	tpCR, safety, cardiovascular AEs
Díaz-Redondo (2019)	254	Retro, record review, MC	P+T+Chemo: 86% taxane + AC, 14% taxane only T+Chemo: 93% taxane+AC, 7% AC only	Critical	Participants with HER2+ eBC.	bpCR, tpCR
Neopearl (Fabbri 2023)	271	Retro, MC	P+T+Chemo: 62.8% taxane + AC, 37.2% taxane without AC, 2.9% carboplatin T+Chemo: 94.8% taxane + AC, 5.2% taxane without AC, 7.5% carboplatin	Critical	≥18 years with histologically confirmed HER2-positive invasive BC, localised extent of disease (Stage II or III according to the AJCC 8th edition).	bpCR, tpCR, safety, cardiotoxicity
Hung (2022)	147	Retro, cohort	AC 100%, docetaxel 100%	Critical	Female HER2+ BC participants.	tpCR, DFS, OS
Jiao (2024)	2,010	Retro, cohort, MC	P+T+Chemo: 89.6% taxane, 10.1% taxane + AC T+Chemo: 54.5% taxane, 45.2% taxane + AC	Critical	Participants 18-80 years of age with HER2-positive eBC.	tpCR, DFS
Little (2020)	176	Retro, case notes	P+T+Chemo: 48% AC + taxane, 52% carboplatin + taxane T+Chemo: 100% AC + taxane	Critical	Stage 1-3 HER2+ BC.	tpCR

Trial	N[a]	Design / follow-up duration (years)	Chemo component (relevant arms)	Bias	Patient population	Key Outcomes
Spring (2018)	121	Retro, record review, MC	AC, P+T+Chemo: AC then taxane P+T+Chemo: 60.4% taxane, 39.6% taxane + carboplatin T+Chemo: AC then taxane	Critical	Participants with HER2-positive invasive BC (Stage I-III).	tpCR, tolerability, dose reduction or delay, discontinuation, hospitalisation
Van der Voort (2022)	1,124	Cohort, registry	P+T+Chemo: 52.5% AC T+Chemo: 79.0% AC	Serious	Stage II-III HER2+ BC participants.	tpCR, BCSS, OS
Vieira (2023)	94	Retro, record review	AC + taxane + cyclophosphamide	Critical	Female adults with clinically diagnosed HER2+ Stage II-III, operable, locally advanced or inflammatory BC.	tpCR, safety
NBRST (Whitworth 2022)	295	Prospective, observational, MC	24.4% AC + taxane, 69.2% taxane, 6.4% other	Critical	Participants aged 18-90 years with eBC without metastatic disease.	tpCR, DMFS, OS

Source: Tables 2-4, 2-5, 2-16 & 2-54, pp44, 51-52, 73-77 & 122-126 of the resubmission.
AEs=adverse events; AR=adaptive randomisation; BC=breast cancer; BCSS=breast cancer specific survival; bpCR=breast pathological complete response; DB=double blind; DDFS=distant disease free survival; DFS=disease free survival; DMFS= distant metastases free survival; DRFS=distant relapse free survival; eBC=early breast cancer; EFS=event free survival; HER2 = human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=in situ hybridisation; MC=multicentre; Mod.=moderate; OL=open label; OS=overall survival; P+T+Chemo = pertuzumab + trastuzumab + chemotherapy; PFS=progression free survival; R=randomised; Retro=retrospective; tpCR=total pathological complete response; T+Chemo = trastuzumab + chemotherapy; yrs=years.
[a] Number of participants in arms relevant to the resubmission.
[b] The NEOSPHERE, PEONY, and TRYPHAENA trials were previously considered by the PBAC. A claim of superior comparative efficacy for P+T+Chemo vs T+Chemo was made on the outcome of pCR (based on the evidence presented in the 4 RCTs and 14 observational studies). A claim of inferior, yet manageable, comparative safety for P+T+Chemo vs T+Chemo was made based on the safety outcomes presented in the 4 RCTs and 14 observational studies).

6.13 In the previous PBAC submission, the ESC considered that the risk of bias in the NEOSPHERE and TRYPHAENA trials was moderate and the risk of bias in the PEONY trial was low (para. 6.10, pertuzumab PSD, March 2020 PBAC meeting). Similar to the NEOSPHERE and TRYPHAENA trials, the I-SPY2 trial was open-label, and the primary endpoint (pCR) was assessed using resected tumours by local pathologists trained in the residual cancer burden method. Therefore, the resubmission proposed that the risk of bias in the I-SPY2 trial was moderate. The evaluation considered assessments of moderate risk of bias for the NEOSPHERE, I-SPY2, and TRYPHAENA trials and low risk of bias for the PEONY trial were reasonable.

6.14 The resubmission did not assess the risk of bias in the observational studies. The risk of bias in the observational studies was assessed during the evaluation and is presented in Table 4.

6.15 Key differences in the RCT eligibility criteria were:

- **Eastern Cooperative Oncology Group (ECOG) performance status:** The NEOSPHERE, PEONY and TRYPHAENA trials required participants to have an ECOG score of 0 or 1. The I-SPY2 trial did not restrict participants by ECOG status.
- **LVEF:** The NEOSPHERE, PEONY and TRYPHAENA trials required participants to have an LVEF ≥55. The I-SPY2 trial did not restrict participants by LVEF.

6.16 Key differences in the RCT participant characteristics were:

- **Race:** Participants in the NEOSPHERE, I-SPY2 and TRYPHAENA trials were predominantly Caucasian (≥72%) whereas all participants in the PEONY trial were Asian.
- **Operable breast cancer:** Approximately 60% of participants in relevant arms of the NEOSPHERE trial had operable breast cancer, compared to approximately 70% in both arms of the PEONY trial, and between 64% and 73% of participants in relevant arms of the TRYPHAENA trial. The I-SPY2 trial did not report on this characteristic.
- **Inflammatory breast cancer**: Between 7% and 9% of participants in relevant arms of the NEOSPHERE trial had inflammatory breast cancer, compared to 5% to 7% in relevant arms of the TRYPHAENA trials. The PEONY trial excluded participants with inflammatory breast cancer and the I-SPY2 trial did not report on this characteristic.
- **Median tumour size:** The median tumour size at clinical breast examination ranged from 50-55 mm in relevant arms of the NEOSPHERE and TRYPHAENA trials, and 34-35 mm in the I-SPY2 trial. The PEONY trial did not report on this characteristic.
- **Hormone receptor status:** Approximately 50% of participants were hormone (oestrogen or progesterone) receptor positive in the NEOSPHERE, PEONY, and TRYPHAENA trials. The rate was slightly higher in the I-SPY2 trial (63%).

6.17 There were differences in the number of neoadjuvant treatment cycles and the chemotherapy provided across the RCTs and observational studies (Table 4).

6.18 There were differences in the definition of pCR across the RCTs and observational studies. The different ways to define pCR are summarised in Table 5. Breast pathological complete response (bpCR) was the primary outcome in the NEOSPHERE trial and the primary efficacy outcome in the TRYPHAENA trial. Total pathological complete response (tpCR) was the primary outcome in the PEONY and I-SPY2 trials and a secondary outcome in the NEOSPHERE and TRYPHAENA trials, and was the outcome reported for the 14 observational studies.

Table 5: Definitions of pCR

Common name	Abbreviation	TMN code	Definition
Breast pathological complete response	bpCR	ypT0/is	Absence of invasive cancer in breast (irrespective of carcinoma in situ). Invasive disease in lymph nodes is permitted.
Total pathological complete response	tpCR	ypT0/is ypN0	Absence of invasive cancer in breast and axillary nodes (irrespective of ductal carcinoma in situ).
German Breast Group pathological complete response	GBG pCR	ypT0 ypN0	Absence of invasive cancer and ductal carcinoma in situ in breast and axillary nodes.

Source: Table 2-17, p78 of the resubmission.
bpCR=breast pathological complete response; GBG=German Breast Group; pCR=pathological complete response; tpCR=total pathological complete response.

Minimal clinically important difference (MCID)

6.19 The resubmission proposed a minimal clinically important difference (MCID) for bpCR and tpCR of 15%. The 15% treatment difference was originally used to determine the sample size of the NEOSPHERE and PEONY trials. The resubmission noted that the FDA and EMA considered that a marked difference in pCR is clinically significant. The resubmission claimed that the regulatory approval for pertuzumab (FDA and EMA) as well as health technology assessment (HTA) approvals were based on the statistically significant improvement in tpCR for P+T+Chemo (docetaxel) vs T+Chemo (docetaxel) in the NEOSPHERE trial; implying that this statistically significant difference was also clinically meaningful. The PBAC previously considered that the MCID of 15% was not adequately justified, noting the role of tpCR as a surrogate measure for patient relevant outcomes was unclear (para. 7.5, pertuzumab, March 2020 PBAC meeting).

Surrogate outcomes

6.20 Appendix A assessed the clinical relevance of pCR as a surrogate measure for prevention of disease recurrence in patients with HER2 positive eBC who are being treated with HER2-targeted therapy in the neoadjuvant and adjuvant settings against the PBAC Framework (Appendix 5 of the PBAC guidelines). The document included responses to the 4 sub-sections recommended in Appendix 5 of the PBAC guideline:

- A5.1 - Define the proposed surrogate measure (PSM) and the target clinical outcome (TCO).

  The PSM was described as pCR and was defined as the absence of residual invasive cancer in the resected breast specimen and in the axillary lymph nodes (ypT0/Tis ypN0). The definition of the PSM was consistent with the definition of total pathological complete response (tpCR) used in the resubmission. The TCO was described as risk of recurrence, which was defined as a composite outcome of disease recurrence, disease free survival (DFS), event free survival (EFS), progression, or death due to any cause. DFS and EFS are surrogate outcomes for overall survival.

- A5.2 – Establish the biological reasoning for the link between the PSM and the TCO, including how pivotal the PSM is to the causation pathway of the TCO, and present epidemiological evidence to support this.

Appendix A concluded it was biologically plausible that patients known to have residual disease will face a higher risk that disease will manifest into invasive disease, and provided several references (Bonadonna 1993, Cameron 1997, Liedtke 2008, Mieog 2007). These references supported a link between residual disease following neoadjuvant treatment + surgery and survival.

Appendix A conducted a pragmatic search of information to justify the relationship between pCR and the risk of disease recurrence specifically relating to pertuzumab and trastuzumab as neoadjuvant treatment for HER2+ eBC. Swain 2020 (abstract) and Swain 2022 (journal article) were the only relevant results. Results from 3 economic models which reported the relationship between pCR and disease recurrence following neoadjuvant treatment of eBC (not limited to pertuzumab and/or trastuzumab) were also included.

- A5.3 – Present randomised trial evidence to support the nature of the PSM-TCO comparative treatment effect relationship.

  Table 1 summarises the results from the PSM-TCO relationship across Swain 2022 and the 3 other references. All the included evidence appears to support the claim that achieving pCR reduces the risk of disease recurrence, although the magnitude of benefit differs across studies.

Table 6: Summary of available evidence reported the risk of disease recurrence in patients with pCR at the neoadjuvant setting, irrespective of treatments received

Study	Study Features	HR for disease recurrence with pCR	Source
Swain 2022	Five RCTs including 1763 patients with HER2+ EBC patients who received pertuzumab, trastuzumab or both in the neoadjuvant setting.	0.35 (0.27–0.46)	Swain 2022, Figure 1A
Symmans 2017	Cohort study with prospective follow-up of patients to test the long-term prognostic performance of residual cancer burden after neoadjuvant chemotherapy	0.44 (0.34 to 0.58) 0.52 (0.40 to 0.69)	Table 2 (HER2 populations) Hazard ratios reported for the residual disease population have been inverted i.e. (1/1.91) to (1/2.25)
Broglio 2016	36 studies with EFS by pCR status representing 5768 patients with HER2-positive breast cancer were included in the patient-level analysis	0.37 (0.32-0.43)	Broglio 2016, Table 2
Cortazar 2014	12 international trials of patients who had neoadjuvant treatment of EBC, with the aim to investigate the potential of pCR as a surrogate endpoint for long-term outcomes	0.39 (0·31–0·50)	Cortazar 2014, Figure 5

Source: Table 6, Appendix A.
EBC = early breast cancer; EFS = event free survival; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; pCR = pathological complete response; RCT = randomised controlled trial.

- A5.4 – Translate the comparative treatment effect on the PSM from the studies included in Part A, Subsection 2.2, to an estimate of the comparative treatment effect for the TCO.

Appendix A applied the hazard ratio from Swain 2022 in the economic model to translate the treatment effect of P+T+Chemo vs T+Chemo in terms of tpCR into invasive disease free survival (iDFS).

6.21 The resubmission noted that the US Food and Drugs Administration (FDA) established an international working group called Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC), which concluded that eradication of tumour from both breast and lymph nodes (i.e., tpCR) was strongly associated with improved survival. The resubmission also noted FDA and European Medicines Agency (EMA) guidance on the use of pCR in breast cancer studies that both conclude that it is reasonably likely that pCR is associated with improved survival outcomes, especially if the improvement in pCR rates is substantial.

6.22 The PBAC previously noted that a meta-analysis of trials assessing neoadjuvant chemotherapy as treatment for eBC reported the prognostic importance of pCR, which correlated with EFS and OS (para 4.3, pertuzumab PSD, March 2019 PBAC meeting).[9] The abstract provided with the March 2019 PBAC submission for pertuzumab as adjuvant treatment for eBC was subsequently published as a complete journal article (Spring 2020).[10] Spring (2020) defined pCR as either ypT0 ypN0 (no invasive or non-invasive residual in breast or nodes) [GBG pCR] or ypT0/is ypN0 (no invasive residual in breast or nodes; non-invasive breast residuals allowed) [tpCR], as suggested by FDA guidelines. If results were available for both definitions, tpCR was utilised. Spring (2020) found that HER2+ participants with pCR following neoadjuvant treatment had significantly better EFS than those with residual disease (HR: 0.32, 95% Probability Interval: 0.15, 0.30).

6.23 Swain (2022) analysed patient-level data from 5 RCTs evaluating trastuzumab, pertuzumab, or both as part of systemic neoadjuvant and adjuvant therapy for HER2-positive early breast cancer and assessed EFS in 1,763 participants. However, Swain (2022) did not describe how relevant studies were identified, selected, and abstracted; thus, it was unknown whether the authors identified and considered all relevant studies. There were imbalances in baseline characteristics and treatment modalities in the included studies of Swain (2022). A multi-trial meta-regression was not possible given the small number of RCTs (N=5).

6.24 The ESC considered the evidence available supported the claim that pCR is likely to be associated with decreased risk of disease recurrence and improved survival outcomes, however noted that the quantification of the surrogate relationship was uncertain. The ESC also noted that the evidence reported HRs that ranged from 0.32 to 0.52 for disease recurrence with pCR. The pre-PBAC response acknowledged that there is a

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

[10] Spring L, Fell G, et al. (2020) Pathologic Complete Response after Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Survival: A Comprehensive Meta-Analysis, Clin Cancer Res, 26:2838-48.

level of uncertainty but argued that the level of uncertainty may be overstated given that the surrogate relationship is supported by data from nearly 50 studies, across more than 8,000 HER2+ eBC patients. The pre-PBAC response also noted the HR at the upper end of the range (0.52) was reported in a single study of only 103 HER2+ patients (Symmans 2017), and Swain (2022) was the most applicable and high quality study.

Inputs to the economic model and financial estimates

6.25 The economic evaluation and budget impact model used the proportion of participants achieving pCR in the 14 observational studies that included anthracycline chemotherapy to estimate the proportion of 'responders' who would not require adjuvant therapy with T-DM1. The economic model used the hazard ratio from Swain (2022) to estimate disease recurrence for participants achieving pCR following neoadjuvant treatment. Data from the NEOSPHERE, PEONY, I-SPY2, and TRYPHAENA trials were not extensively used in the economic evaluation or budget impact model. The economic model included the percentage of patients experiencing diarrhoea from the PEONY trial to estimate QALY losses due to adverse events, and the percentage of patients achieving pCR in the NEOSPHERE trial was used in sensitivity analysis.

Comparative effectiveness

RCTs

6.26 Table 7 presents the results for bpCR in the RCTs that collected this outcome.

Table 7: Results of bpCR across the trials

Trial ID	Intervention		Comparator		Difference (95% CI)	p value
	n/N (%)	95% CI	n/N (%)	95% CI		
P+T+Chemo (docetaxel) vs T+Chemo (docetaxel), 4 neoadjuvant HER2 therapy cycles						
NEOSPHERE	49/107 (45.8)	36.1, 55.7	31/107 (29.0)	20.6, 38.5	**16.8% (3.5, 30.1)**	**0.0141**
PEONY (IRC assessed)	92/219 (42.0)	35.39, 48.85	26/110 (23.6)	16.06, 32.68	**18.37% (7.60, 29.15)**	**0.0010**
P+T+Chemo (3+3) vs P+T+Chemo (6), 6 neoadjuvant HER2 therapy cycles						
TRYPHAENA	45/73 (61.6)	49.5, 72.8	51/77 (66.2)	54.6, 76.6	N/A	N/A

Source: Tables 2-19, 2-26 & 2-33, pp82, 88 & 92 of the resubmission. **Bold** indicates statistically significant results.
3+3=3 x (5-fluorouracil + epirubicin + cyclophosphamide) cycles then 3 x docetaxel cycles; 6=6 x docetaxel + carboplatin cycles; bpCR = breast pathological complete response; CI = confidence interval; IRC = Independent Review Committee; n = number of participants with event; N = total participants in group; P+T+Chemo = pertuzumab + trastuzumab + chemotherapy; T+Chemo = trastuzumab + chemotherapy.

6.27 In the NEOSPHERE trial, participants receiving P+T+Chemo had a bpCR rate of 45.8% compared to 29.0% in participants receiving T+Chemo, a statistically significant difference of 16.8% (95%CI: 3.5, 30.1). In the PEONY trial, a significantly greater proportion of participants in the P+T+Chemo arm achieved the secondary endpoint of bpCR responder (as assessed by an independent review committee) compared to participants in the T+Chemo arm (42.0% vs 23.6%; difference in response rates of 18.37%, p=0.0010). The bpCR responder rate in the TRYPHAENA trial, where both treatment arms presented received 6 cycles of P+T+Chemo, was over 60%.

6.28 Table 8 presents the results for tpCR in the RCTs that collected this outcome.

Table 8: Results of tpCR across the trials

Trial ID	Intervention		Comparator		Difference (95% CI)	p value
	n/N (%)	95% CI	n/N (%)	95% CI		
P+T+Chemo vs T+Chemo, 4 neoadjuvant HER2 therapy cycles[a]						
NEOSPHERE	42/107 (39.3)	30.0, 49.2	23/107 (21.5)	14.1, 30.5	17.8%[b] (4.6, 31.0)	0.008[b]
PEONY	86/219 (39.3)	32.76, 46.08	24/110 (21.8)	14.51, 30.70	**17.45% (6.89, 28.01)**	**0.0014**
I-SPY2	56%	42, 70	25%	11, 38	**99.9%** probability that P+T+Chemo was superior to H+Chemo and a **97%** predictive probability of superiority in a 300-participant Phase 3 trial.	
P+T+Chemo (3+3) vs P+T+Chemo (6), 6 neoadjuvant HER2 therapy cycles						
TRYPHAENA	41/73 (56.2)	NR	49/77 (63.6)	NR	NA	NA

Source: Tables 2-19, 2-26, 2-32 & 2-35, pp82, 88, 92 &93 of the resubmission; p93 of the resubmission. **Bold** indicates statistically significant results.

3+3=3 x (5-fluorouracil + epirubicin + cyclophosphamide) cycles then 3 x docetaxel cycles; 6=6 x docetaxel + carboplatin cycles; CI = confidence interval; HER2= human epidermal growth factor receptor 2; n = number of participants with event; N = total participants in group; NA=not applicable; NR=not reported; P+T+Chemo= pertuzumab + trastuzumab + chemotherapy; T+Chemo=trastuzumab + chemotherapy; tpCR= total pathological complete response.

[a] Chemotherapy in the NEOSPHERE and PEONY trials was docetaxel; chemotherapy in the I-SPY2 trial was weekly paclitaxel + 4 x 3-weekly trastuzumab [+/-pertuzumab]], followed by 3 4 cycles of doxorubicin + cyclophosphamide

[b] Calculated post-hoc using RevMan, not adjusted for multiplicity.

6.29 In the NEOSPHERE trial, the P+T+Chemo arm had a higher rate of tpCR than the T+Chemo arm (difference of 17.8%; 95%CI: 4.6, 31.0; p=0.008); however, these results were calculated post-hoc and not adjusted for multiplicity. In the PEONY trial, a significantly greater proportion of participants in the P+T+Chemo arm achieved the primary endpoint of tpCR response (as assessed by IRC) compared to participants in the T+Chemo arm (39.3% vs 21.8%; difference in response rates of 17.45%, p=0.0014). In the I-SPY2 adaptive-randomisation trial, 56% of participants receiving P+T+Chemo achieved tpCR compared to 25% of participants who received T+Chemo. The mean differences exceeded the stated MCID of 15%, although the lower 95% confidence intervals (CIs) for tpCR of 6.9% in PEONY and 4.6% in NEOSPHERE were substantially lower than the MCID of 15%. Over 55% of participants in relevant arms of the TRYPHAENA trial achieved tpCR.

6.30 Table 9 presents PFS and DFS by tpCR status (achieved vs not achieved) in the NEOSPHERE trial. Although iDFS based on tpCR status was a key input in the economic model, these NEOSPHERE data were not used in the economic model. Instead, the hazard ratio from Swain (2022) was used to estimate DFS based on tpCR.

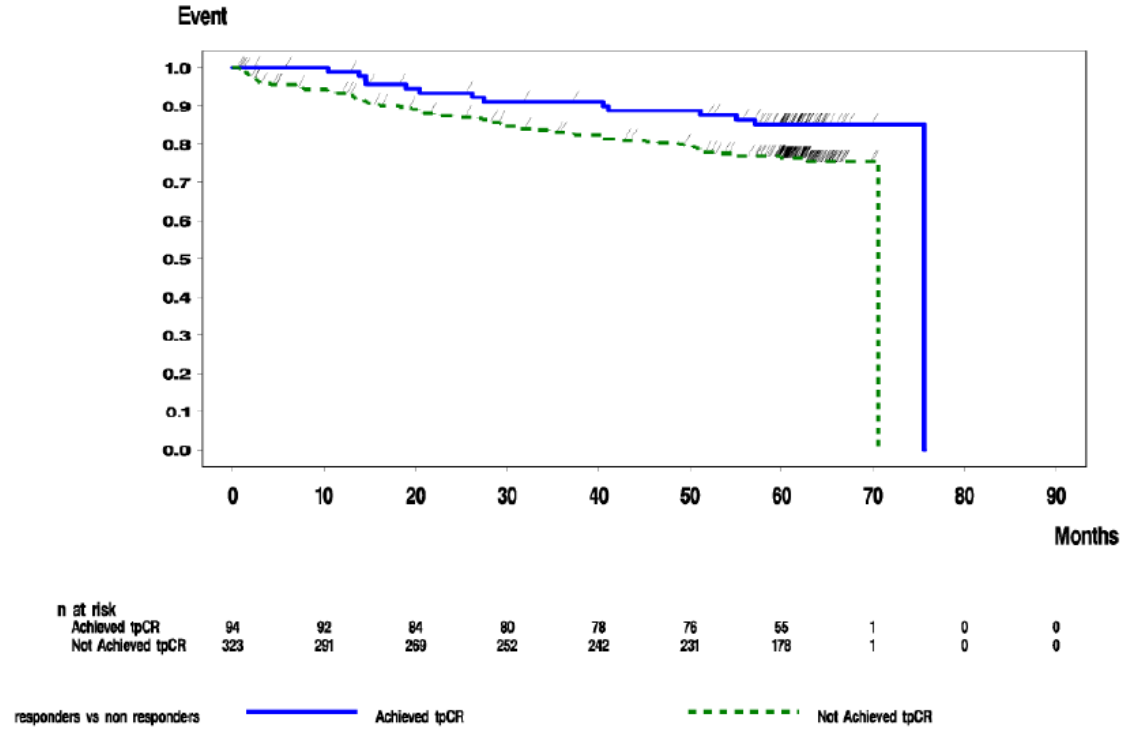
Table 9: Results of PFS and DFS in the NEOSPHERE trial by tpCR status

Trial ID	Achieved tpCR		Did not achieve tpCR		Difference in median	P value	Hazard ratio (95% CI)
	n/N (%)	Median time to event (95% CI)	n/N (%)	Median time to event (95% CI)			
P+T+Chemo (docetaxel) vs T+Chemo (docetaxel), 4 neoadjuvant HER2 therapy cycles							
PFS							
NEOSPHERE	14/94 (14.9)	Not reached	73/323 (22.6)	Not reached	Not estimable	0.046	0.54 (0.29, 1.00)
DFS							
NEOSPHERE	14/94 (14.9)	Not reached	60/298 (20.1)	Not reached	Not estimable	0.218	0.68 (0.36, 1.26)

Source: Table 2-23, p85 of the resubmission; t_ttev2_dfs_tpcrvs_i, p166 of the NEOSPHERE CSR Feb 2015.
CI=confidence interval; DFS=disease free survival; HER2=human epidermal growth factor receptor 2; n=number with event; N=total participants in group; PFS=progression free survival; P+T+Chemo=pertuzumab + trastuzumab + chemotherapy; T+Chemo=trastuzumab + chemotherapy; tpCR=total pathological complete response.

6.31 Figure 1 presents PFS by tpCR status (achieved vs not achieved) in the NEOSPHERE trial. The NEOSPHERE CSR did not include a Kaplan Meier figure for DFS by tpCR status.

Figure 1: Progression free survival by tpCR status in the NEOSPHERE trial



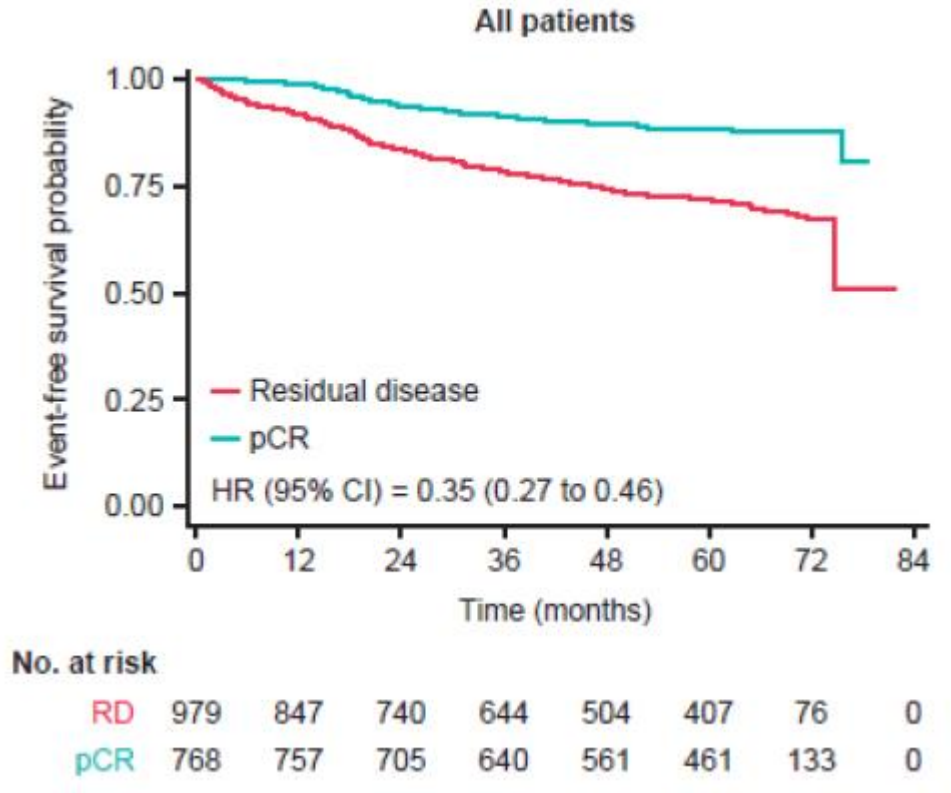
Source: Figure 2-7, p86 of the resubmission.
CI=confidence interval; H=trastuzumab; ITT=intent to treat; P=pertuzumab; PFS=progression-free survival; T=docetaxel

6.32 Swain (2022) found that participants with pCR had decreased risk of an EFS event versus those with residual disease (HR: 0.35, 95% CI: 0.27-0.46). Swain 2022 defined pCR as the absence of residual invasive cancer in the resected breast specimen and in

the axillary lymph nodes (ypT0/Tis ypN0) after neoadjuvant systemic therapy (i.e., tpCR).

6.33 Figure 2 shows EFS for participants included from the 5 RCTs in Swain (2022) based on pCR status. Similar results were observed for subgroup analyses based on disease stage (II or III), lymph node status (positive or negative), hormone receptor status (positive or negative), or HER2 treatment types (neoadjuvant and adjuvant trastuzumab, neoadjuvant pertuzumab and adjuvant trastuzumab, or neoadjuvant and adjuvant pertuzumab).[11] Swain (2022) stated that the number of overall survival events was too low to perform a robust analysis of that outcome.

Figure 2: Event-free survival in patients with pCR after neoadjuvant systemic HER2-targeted therapy



Source: Figure 1A, Swain 2022.
HER2=Human Epidermal Growth Factor Receptor 2; HR=hazard ratio; pCR= pathological complete response; RD=residual disease.

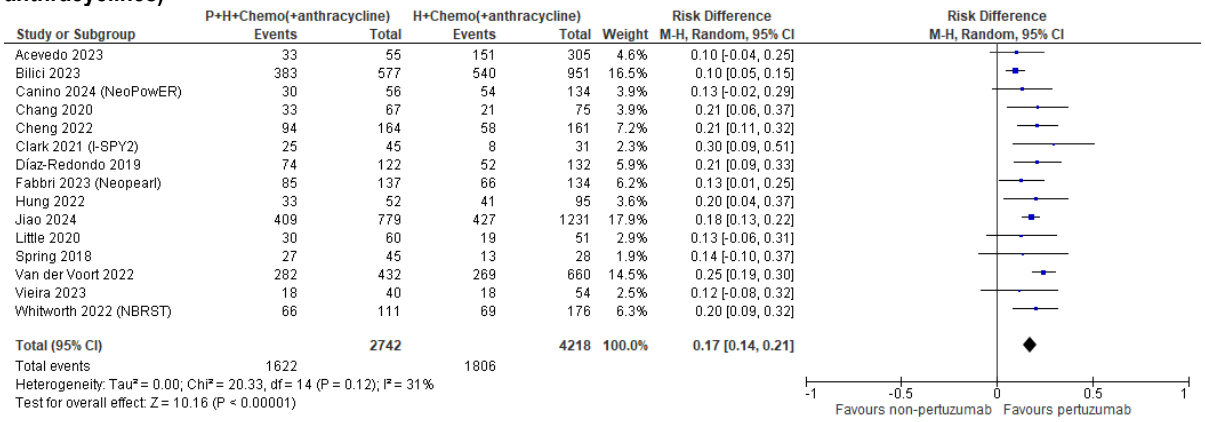
Observational studies

6.34 Figure 3 presents the response rates (tpCR) from the I-SPY RCT and 14 comparative studies of P+T+Chemo vs T+Chemo (including anthracyclines). Out of 2,742

[11] Swain SM, Macharia H, Cortes J, et al. 2022. Event-Free Survival in Patients with Early HER2-Positive Breast Cancer with a Pathological Complete Response after HER2-Targeted Therapy: A Pooled Analysis. Cancers (Basel) 14(20). Available at: 10.3390/cancers14205051

participants receiving neoadjuvant P+T+Chemo, 1,622 (59.2%) achieved tpCR, compared with 1,806/4,218 (41.8%) of participants receiving neoadjuvant T+Chemo.

Figure 3: Forest plot of tpCR rates from the comparative studies of P+H+Chemo vs H+Chemo (including anthracyclines)



Source: Figure 2-10, p133 of the resubmission.
CI=confidence interval; M-H=Mantel-Haenszel.

6.35 The random effects meta-analysis of pCR rates from the 15 studies resulted in a weighted proportion of responders in the P+T+Chemo and T+Chemo arms of 59.2% and 41.8%, respectively. The test for heterogeneity found no significant difference across the trials (P=0.12).

6.36 The difference between P+T+Chemo vs T+Chemo among the observational studies involving a range of chemotherapies was similar to that in the NEOSPHERE and PEONY trials where docetaxel was administered. The ESC noted the limitations of the observational studies but considered the additional data presented helped to address the PBAC's previous concern regarding the effectiveness of pertuzumab when used with anthracyclines.

Adjuvant pertuzumab

6.37 The submission did not provide evidence for use of pertuzumab as adjuvant treatment as the submission request was for neoadjuvant treatment only. However, the PBAC has previously considered evidence from the APHINITY trial, an RCT comparing P+T+Chemo vs T+Chemo, which showed the iDFS event-free rates for node-positive patients were 89.88% vs. 86.68% at 4 years (difference of 3.2%), for Ptz+T+Chemo versus T+Chemo, respectively. Updated results of 8-year iDFS in the node-positive cohort showed an absolute improvement of 4.9% favouring pertuzumab (86.1% vs. 81.2%; HR: 0.72,95% CI: 0.60-0.87])[12]. The APHINITY trial did not include patients previously treated in the neoadjuvant setting, and therefore the outcomes

[12] Loibl et al (2024) Adjuvant Pertuzumab and Trastuzumab in Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer in the APHINITY Trial: Third Interim Overall Survival Analysis With Efficacy Update. *Journal of clinical Oncology Volume 42, Number 31* https://doi.org/10.1200/JCO.23.02505

are only directly relevant to patients initially considered node negative, or who elect not to undergo neoadjuvant treatment prior to surgery.

6.38 The PEONY trial also included adjuvant treatment with P+T following neoadjuvant P+T+Chemo. PEONY was similar to the NEOSPHERE study except that the randomised treatment allocation in the neoadjuvant setting continued in the adjuvant setting, regardless of pCR. However, the generalisability of PEONY was limited as it was a relatively small trial in an entirely Asian population. In addition, no treatment decisions were made based on the pCR in either arm (i.e. no patients switched to T-DM1). The longer term follow-up indicated an improvement in 5-year event-free survival (84.8% with pertuzumab and 73.7% with placebo [(HR: 0.53; 95% CI: 0.32-0.89], while 5-year disease-free survival rates were 86.0% and 75.0%, respectively (HR: 0.52; 95% CI: 0.30-0.88). However, the extent of benefit from pertuzumab treatment in the adjuvant setting is unclear from PEONY as patients in the control arm did not receive neoadjuvant pertuzumab.

Comparative harms

RCTs

6.39 Table 10 presents key safety data from the neoadjuvant periods of each included trial; serious adverse events, Grade ≥3 adverse events, discontinuations, and event types highlighted previously by the PBAC in the March 2020 submission.

6.40 The PBAC previously noted a significant increase in left ventricular systolic dysfunction in the NEOSPHERE trial in the overall trial period (8.4% and 1.9% of participants receiving P+T+Chemo and T+Chemo, respectively) (para. 7.9, pertuzumab PSD, March 2020 PBAC meeting). However, there was not a significant increase in left ventricular systolic dysfunction over the neoadjuvant trial period (Table 10).

Table 10: Key safety data from the included trials (neoadjuvant period)

	Intervention, N(%)	Comparator, N(%)	Relative risk (95%CI)	p-value[a]
P+T+Chemo vs T+Chemo, 4 neoadjuvant HER2 therapy cycles[b]				
NEOSPHERE				
SAEs	12 (11.2)	18 (16.8)	0.67 (0.34, 1.32)	0.24
AEs leading to discontinuation	2 (1.9)	0	5.00 (.24. 102.93)	0.30
Grade ≥3 AEs	65 (60.7)	80 (74.8)	**0.81 (0.67, 0.98)**	**0.03**
Diarrhoea (Grade ≥3)	6 (5.6)	4 (3.7)	NR	NR
Diarrhoea (any grade)	49 (45.8)	36 (33.6)	NR	NR
LVSD or CHF (any grade)	3 (2.8)	1 (0.9)	NR	NR
Infusion-related reactions (any grade)	7 (6.5)	5 (4.7)	NR	NR
PEONY				
SAEs	22 (10.1)	9 (8.2)	1.23 (0.15, 2.59)	0.58
AEs leading to discontinuation	1 (0.5)	0	1.52 (0.06, 37.02)	0.80
Grade ≥3 AEs	106 (48.6)	46 (41.8)	1.16 (0.90, 1.51)	0.25
Diarrhoea (Grade ≥3)	Less than 3% difference		NR	NR
Diarrhoea (any grade)	84 (38.5)	18 (16.4)	NR	NR
LVSD or CHF (any grade)[c]	0 (0)	0 (0)	NR	NR
Infusion-related reactions (any grade)	48 (22.0)	10 (9.1)	NR	NR
I-SPY2				
SAEs	NR	NR	NR	NR
AEs leading to discontinuation	Pac. period: 3 (6.7) Ant. period: 2 (5.0)	0 0	NR	NR
Grade ≥3 AEs	Pac. period: 5 (11) Ant. period: 4 (10)	3 (9.7) 3 (10.7)	NR	NR
Diarrhoea (Grade ≥3)	Pac. period: 0 Ant. period: 0	1 (3.2) 0	NR	NR
Diarrhoea (any grade)	Pac. period: 35 (77.8) Ant. period: 8 (20.0)	15 (48.4) 6 (21.4)	NR	NR
LVSD or CHF (any grade)	NR	NR	NR	NR
Infusion-related reactions (any grade)	Pac. period: 2 (4.4) Ant. period: 0 (0)	4 (12.9) 0 (0)	NR	NR
P+T+Chemo (3+3) vs P+T+Chemo (6), 6 neoadjuvant HER2 therapy cycles				
TRYPHAENA				
SAEs	20 (27.8)	27 (35.5)	N/A	N/A
AEs leading to discontinuation	4 (5.6)	6 (7.9)		
Grade ≥3 AEs	50 (69.4)	56 (73.7)	N/A	N/A
Diarrhoea (Grade ≥3)	3 (4.2)	9 (11.8)	N/A	N/A
Diarrhoea (any grade)	44 (61.1)	55(72.4)	N/A	N/A
LVSD or CHF (any grade)	4 (5.6)	2 (2.6)	N/A	N/A
Infusion-related reactions (any grade)	3 (4.2)	4 (5.3)	N/A	N/A

Source: Tables 2-36, 2-37, 2-38, 2-41, 2-42, 2-43, 2-44, 2-47, 2-48, 2-49 & 2-51; pp94-99, 102-106, 109-114 of the resubmission; NEOSPHERE, TRYPHAENA, PEONY CSRs; Clark 2021.

AE = adverse event; Ant.=anthracycline; chemo = chemotherapy; CHF= congestive heart failure; CI = confidence interval; LVSD=left ventricular systolic dysfunction; N = number experiencing event; N/A = not applicable; NR = not reported; P = pertuzumab; Pac.=paclitaxel; SAE = serious adverse event; T = trastuzumab.

[a] Calculated post-hoc using RevMan.

[b] Chemotherapy in the NEOSPHERE and PEONY trials was docetaxel; chemotherapy in the I-SPY2 trial was weekly paclitaxel + 4 x 3-weekly trastuzumab [+/-pertuzumab]], followed by 3 4 cycles of doxorubicin + cyclophosphamide

[c] LVSD only

6.41 During the neoadjuvant period, there was one death in the P+T+Chemo arm of the NEOSPHERE trial (fulminant hepatitis) that was considered possibly related to study treatment. There was one death in the P+T+Chemo arm of the PEONY trial (suicide) and one death in the P+T+Chemo arm of the I-SPY trial (respiratory failure); both were considered unrelated to study treatment. There were no deaths in the neoadjuvant period of the TRYPHAENA trial.

Observational studies

6.42 Table 11 presents key safety data from the 14 observational studies, specifically serious adverse events, Grade ≥3 adverse events, discontinuations, and event types highlighted previously by the PBAC in the March 2020 submission.

Table 11: Summary of adverse events from the comparative studies of P+T+Chemo vs T+Chemo (including anthracyclines)

Study	P+T+Chemo n/N (%)	T+Chemo n/N (%)	OR [95% CI] OR< 1; RD<0 favours pertuzumab arm	RD [95% CI]
(Bilici 2023)				
Diarrhoea (Grade ≥3)	7/577 (1.2)	8/951 (0.8)	1.45 [0.52, 4.01]	0.00 [-0.01, 0.01]
Diarrhoea (any grade)	156/577 (27.0)	152/951 (16.0)	**1.95 [1.51, 2.51]**	**0.11 [0.07, 0.15]**
(Cheng 2022)[a]				
Diarrhoea (any grade)	65/321 (20.2)	NR	NE	NE
Serious cardiovascular AEs	0	NR	NE	NE
Neopearl (Fabbri 2023)				
Diarrhoea(Grade ≥3)	4/137 (2.9)	2/134 (1.5)	1.98 [0.36, 11.02]	0.01 [-0.02, 0.05]
Diarrhoea (any grade)	39/137 (28.5)	47/134 (35.1)	0.74 [0.44, 1.23]	-0.07 [-0.18, 0.04]
Cardiologic events Grade ≥3	5/137 (3.6)	2/134 (1.5)	2.50 [0.48, 13.12]	0.02 [-0.02, 0.06]
Cardiologic events, any grade	14/137 (10.2)	6/134 (4.4)	2.43 [0.90, 6.52]	0.06 [0.00, 0.12]
LVEF decline	14/137 (10.2)	10/134 (7.5)	1.41 [0.60, 3.30]	0.03 [-0.04, 0.10]
(Spring 2018)[b]				
Treatment discontinuation	7/45 (16)	3/28 (11)	1.54 [0.36, 6.50]	0.05 [-0.11, 0.21]
Cardiac outcomes (after a median follow-up of 60 months; following adjuvant therapy)				
Symptomatic cardiac LVEF dysfunction	2/45 (4.4)	0	3.28 [0.15, 70.77]	0.04 [-0.03, 0.12]
LVEF decrease >20%	6/45 (13.3)	5/28 (17.9)	0.71 [0.19, 2.58]	-0.05 [-0.21, 0.12]
Decrease of LVEF <50% with absolute reduction of ≥10% from baseline	3/45 (7)	1/28 (4)	1.93 [0.19, 19.51]	0.03 [-0.08, 0.14]
(Vieira 2023)				
Grade 3 AEs	4/40 (10.0)	3/54 (5.6)	1.89 [0.40, 8.96]	0.04 [-0.06, 0.15]
Diarrhoea (any grade)	17/40 (42.5)	11/54 (20.4)	**2.89 [1.16, 7.19]**	**0.22 [0.03, 0.41]**
Decline of ≥10% in LVEF from baseline post-NA therapy	19/40 (47.5)	26/54 (48.2)	0.97 [0.43, 2.21]	-0.01 [-0.21, 0.20]
LVEF <50% post-NA therapy	1/40 (2.5)	4/54 (7.4)	0.32 [0.03, 2.98]	-0.05 [-0.14, 0.04]
(Canino 2024)[b]				
Significant LVEF reduction events	1/111 (0.9)	2/94 (2)	0.42 [0.04, 4.69]	-0.01 [-0.05, 0.02]

Source: Table 2-57, pp134-136 of the resubmission

AC=doxorubicin and cyclophosphamide; AE=adverse event; CI=confidence interval; LVEF=left ventricular ejection fraction; NE=not estimable; NR=not reported; OR=odds ratio; P+T+Chemo= pertuzumab + trastuzumab + chemotherapy; post-NA=post neoadjuvant; RD=risk difference; T+Chemo= trastuzumab + chemotherapy.

[a] The safety evaluation by Cheng 2022 was limited to participants in the pertuzumab containing arm only who had complete records for AEs (n=321/560), regardless of backbone chemotherapy received, and was based on AEs experienced during neoadjuvant therapy.

[b] Safety outcomes from Canino 2024 (with the exception of the cardiac safety analysis) were reported in the source document according to number/proportion of events (rather than participants) and hence are not presented herein.

6.43 The resubmission claimed that overall, the tolerability of P+T+Chemo appeared similar to T+Chemo. Serious adverse events and Grade ≥3 AEs were lower for P+T+Chemo vs T+Chemo in the NEOSPHERE and I-SPY2 trials but higher for P+T+Chemo vs T+Chemo in the PEONY trial over the neoadjuvant period. Serious adverse events and discontinuations were higher in the TRYPHAENA trial, where participants received 6 cycles of P+T+Chemo, compared to the RCTs that included 4 cycles of HER2 targeted treatment. Supplementary evidence from the observational studies was consistent with the RCTs.

6.44 During the overall study period of NEOSPHERE, left ventricular dysfunction or congestive heart failure (adverse event of special interest) occurred in numerically more P+T+Chemo treated participants (8.4% vs 1.9%), as did Grade ≥3 diarrhoea events (6.5% vs 3.7%). Diarrhoea events (any grade) were also among the most common events occurring in the pertuzumab arms of the PEONY, TRYPHAENA and I-SPY2 trials. However, treatment discontinuations due to AEs were low and modifications/interruptions due to AEs were generally similar across treatment arms of the included studies.

Benefits/harms

6.45 A summary of the comparative benefits and harms for P+T+Chemo versus T+Chemo is presented in Table 12.

Table 12: Summary of comparative benefits and harms for P+T+Chemo and T+Chemo

Trial	P+T+Chemo n/N	T+Chemo n/N	RR (95% CI)	Event rate/100 patients[a]		RD (95% CI)
				P+T+Chemo	T+Chemo	
Benefits						
bpCR						
NEOSPHERE	49/107	31/107	1.58 (1.10, 2.27)	46	29	17 (4, 30)
PEONY	92/219	26/110	1.78 (1.23, 2.57)	42	24	18 (8, 29)
tpCR						
NEOSPHERE	42/107	23/107	1.83 (1.18, 2.81)	39	21	18 (6, 30)
PEONY	86/219	24/110	1.80 (1.22, 2.66)	39	22	17 (7, 28)
Meta-analysis of I-SPY2 and 14 studies, I^2=31%[b]	1622/2742	1806/4218	1.38 (1.32, 1.45)	59	43	16 (14, 19)
Progression free survival (median duration of follow up 60 months)						
	P+T+Chemo	**T+Chemo**	**Absolute Difference**			**HR (95% CI)**
NEOSPHERE						
Progressed, n (%)	17/107 (15.9)	19/107 (17.8)	-			0.69 (0.34, 1.40) p=0.298
Median PFS, months (95% CI)	Not reached	Not reached	Not estimable			
% not progressed at 1 year (95% CI)	96% (92, 100)	98% (95, 100)	-2%			
% not progressed at 5 years (95% CI)	86% (77, 91)	81 (71, 87)	5%			
Disease free survival (median duration of follow up 60 months)						
NEOSPHERE						
Events, n/N (%)	15/107 (14.9)	18/107 (17.5)	-			0.60 (0.28, 1.27) p=0.181
Median DFS, months (95% CI)	Not reached	Not reached	Not estimable			
% without disease at 1 year (95% CI)	96% (92, 100)	95% (91, 99)	1%			
% without disease at 5 years (95% CI)	84% (72, 91)	81% (72, 88)	3%			
PEONY						
Events, n/N (%)	32/219 (14.6)	27/110 (24.5)	-			0.53 (0.32, 0.89) p=0.014
Median DFS, months (95% CI)	Not reached	Not reached	Not estimable			
% without disease at 1 year (95% CI)	98% (97, 100)	90% (85, 96)	8%			
% without disease at 5 years (95% CI)	85% (80, 90)	74% (65, 82)	11%			
Overall survival (median duration of follow up 60 months)						
PEONY						
Events, n/N (%)	12/219 (5.5)	11/110 (10.0)	-			0.53 (0.23, 1.19) P=0.118
Median DFS, months (95% CI)	Not reached	Not reached	Not estimable			
% alive at 1 year (95% CI)	100 (99, 100)	100 (100, 1000)	0%			
% alive at 5 years (95% CI)	94% (90, 97)	90 (84, 96)	4%			
Harms						

	P+T+Chemo n/N	T+Chemo n/N	RR (95% CI)	Event rate/100 patients[a]		RD (95% CI)
				P+T+Chemo	T+Chemo	
Serious Adverse Events (neoadjuvant treatment period)						
NEOSPHERE	12/107	18/107	0.67 (0.34, 1.32)	11	17	-0.06 (-0.15, 0.04)
PEONY	22/218	9/110	1.29 (0.59, 2.59)	10	8	0.02 (-0.05, 0.08)
I-SPY2-PTP	NR	NR	-	-	-	-
I-SPY2-AC	NR	NR	-	-	-	-
Adverse events of Grade ≥3 severity (neoadjuvant treatment period)						
NEOSPHERE	65/107	80/107	0.81 (0.67, 0.98)	61	75	-0.14 (-0.26, -0.02)
PEONY	106/218	46/110	1.16 (0.90, 1.51)	49	42	0.07 (-0.05, 0.18)
I-SPY2-PTP	5/45	3/31	1.15 (0.30, 4.46)	11	10	0.01 (-0.12, 0.15)
I-SPY2-AC	4/40	3/28	0.93 (0.23, 3.85)	10	11	-0.01 (-0.15, 0.14)
Diarrhoea of Grade ≥3 severity (neoadjuvant treatment period)						
NEOSPHERE	6/107	4/107	1.50 (0.44, 5.17)	6	4	0.02 (-0.04, 0.08)
PEONY	NR	NR	-	-	-	-
I-SPY2-PTP	0	1/31	0.23 (0.01, 5.51)	NE	3	-0.03 (-0.11, 0.05)
I-SPY2-AC	0	0	NE	NE	NE	NE
Left ventricular systolic dysfunction (any grade) (overall study period)						
NEOSPHERE	3/107	0	7.00 (0.37, 133.90)	3	NE	0.03 (-0.01, 0.06)
PEONY	0	0	NE	NE	NE	NE
I-SPY2-PTP	NR	NR	-	-	-	-
I-SPY2-AC	NR	NR	-	-	-	-

Source: Tables 2-19, 2-22, 2-32, 2-33, 2-36, 2-38, 2-39, 2-48, & 2-52, pp82, 84-85, 92, 94, 99, 101,111 & 115 of the resubmission; pp149-150, NEOSPHERE CSR Feb 2015, Table 11, PEONY CSR March 2022, Clark 2021.

AC=anthracycline; HR = hazard ratio; PBO = placebo; PTP=pertuzumab + trastuzumab + paclitaxel; RD = risk difference; RR = risk ratio

[a] Neoadjuvant period: NEOSPHERE = 4 cycles (12 weeks); PEONY = 6 cycles (18 weeks); I-SPY2-PTP = 4 cycles (12 weeks); I-SPY2-AC = 4 cycles (8-12 weeks at treating physicians' discretion); Meta-analysis = neoadjuvant period varied across trials and studies.

6.46 On the basis of direct evidence presented by the submission, for every 100 patients treated with P+T+Chemo in comparison with T+Chemo in the neoadjuvant setting:

- Approximately 17-18 additional patients would have breast pathological complete response (absence of invasive cancer in the breast, but invasive disease in the lymph nodes is permitted).
- Approximately 16-18 additional patients would have total pathological complete response (absence of invasive cancer in the breast and axillary lymph nodes).
- Approximately 11 additional patients would remain disease-free after 5 years (based on the PEONY trial). The NEOSPHERE trial did not observe a significant improvement in the number of patients remaining disease free or surviving overall.
- There would be no difference in overall survival after 5 years.
- Up to 2 additional patients would experience a serious adverse event (based on the PEONY trial).
- Up to 7 additional patients would experience an adverse event of Grade ≥3 severity (severe or disabling or requires hospitalisation) (based on the PEONY trial).

- Up to 2 additional patients would experience diarrhoea of Grade ≥3 severity (diarrhoea that is severe or disabling or requires hospitalisation) (based on the NEOSPHERE trial).
- Approximately 3 additional patients would experience left ventricular systolic dysfunction (based on the NEOSPHERE trial).

Clinical claim

6.47 The resubmission described P+T+Chemo as superior in terms of efficacy compared to T+Chemo for patients with high risk eBC, when added to trastuzumab and chemotherapy in the neoadjuvant setting. The efficacy claim was unchanged from the March 2020 submission. The evaluation considered this claim was adequately supported but the magnitude of the effect was uncertain. The ESC considered that the clinical claim of superior efficacy based on improvement in the rates of pCR was reasonable, but noted that pCR was a surrogate endpoint for risk of recurrence and survival outcomes. The ESC considered the evidence supported the claim that pCR is likely to be associated with decreased risk of disease recurrence and improved survival outcomes, however noted that the quantification of the surrogate relationship was uncertain.

6.48 The resubmission described P+T+Chemo as inferior, yet manageable, comparative safety to T+Chemo. The March 2020 submission made a claim of non-inferior safety. The ESC considered the claim of inferior safety was reasonable.

6.49 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.50 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.51 The resubmission presented a modelled economic evaluation comparing P+T+Chemo versus T+Chemo in the neoadjuvant setting for patients with HER2-positive high-risk eBC. The type of economic evaluation presented was a cost-effectiveness and cost-utility analysis. The economic evaluation was changed from the March 2020 submission and was largely based on the economic model presented for T-DM1 (November 2019 submission) as an adjuvant treatment for patients with eBC and residual disease. A neoadjuvant decision tree was added to the T-DM1 Markov structure and an additional data were added to reflect survival following pCR (using the HR from Swain 2022).

6.52 Table 13 summarises the key components of the economic evaluation.

Table 13: Summary of model structure, key inputs and rationale

Component	Summary (March 2025 resubmission)
Treatments	Neoadjuvant: P+T+Chemo vs T+Chemo Adjuvant: T-DM1 or trastuzumab

Component	Summary (March 2025 resubmission)
	Subsequent therapies: Locoregional recurrence: trastuzumab Distance recurrence: T-DM1 or T-DXd or P+T
Time horizon	40 years in the model base case.
Outcomes	Life years and QALYs gained
Methods used to generate results	Decision tree to reflect neoadjuvant treatment + Markov model. This approach allowed for adjuvant treatment with T-DM1, which is used in clinical practice.
Health states	6 health states: iDFS, locoregional recurrence, remission, metastatic recurrence (1st line mBC and 2nd line mBC), death). Metastatic recurrence was stratified by time to relapse (<18 months or ≥18 months). iDFS was stratified by on/off treatment. This was consistent with other models for eBC.
Cycle length	1 week
Population	Mean age 58.5 years and weight 74.5 kg (IPSOS 2018). Patients with locally advanced, inflammatory or early stage HER2 positive breast cancer. The reference to support mean age and weight (IPSOS 2018) *was provided with the PSCR.*
Probabilities in decision tree	Response rates (tpCR) for P+T+Chemo - Responders: 59.2% - Non-responders subsequently receiving T-DM1: 30.6% - Non-responders subsequently receiving adjuvant trastuzumab:10.2% Response rates (tpCR) for T+Chemo: - Responders: 41.8% - Non-responders subsequently receiving T-DM1: 43.7% - Non-responders subsequently receiving adjuvant trastuzumab:14.6% Based on a meta-analysis of studies of neoadjuvant regimens containing anthracycline chemotherapy (14 observational studies and the I-SPY2 trial) (Figure 3Table 8) and an assumed [redacted]% uptake rate for T-DM1.
Transition probabilities in Markov model	iDFS to locoregional recurrence (non-responders) The KATHERINE trial (investigating TDM-1 vs trastuzumab in eBC). The risk of disease recurrence (HR) in patients with pCR from neoadjuvant therapy relative to those who had residual disease (non-responders) was based on Swain (2022). Locoregional recurrence to remission Proportion of patients leaving iDFS and experiencing a locoregional recurrence was based on the KATHERINE trial. Remission to 1st line mBC Remission to metastatic recurrence was based on Hamilton (2015). Hamilton (2015) estimated the risk of second malignancy post adjuvant radiation therapy. These patients were treated with RT and/or systemic chemotherapy and/or hormone therapy. However, no patients received targeted therapy. Remission to death The KATHERINE trial. The CLEOPATRA trial was used in the mBC pertuzumab PBAC 2014 submission. 1st line mBC to 2nd line mBC and death; 2nd line mBC to death Metastatic recurrence to progression and death was based on the EMILIA (investigating TDM-1 in mBC), CLEOPATRA (investigating P+T+Chemo in mBC), and DESTINY Breast- DB03 (DB03) (investigating T-DXd in mBC) trials. The resubmission assumed an uptake rate of [redacted]% for (T-DXd) in each eligible population. The previous submission did not use T-DXd in the economic model. [redacted]All cause mortality All-cause mortality rates were based on ABS Life Tables.
Extrapolation method	Recurrence, progression and survival Kaplan-Meier data was used for iDFS from the KATHERINE trial until median follow-up (truncation point) (probability of remaining in iDFS: 41.2 months), and then independent exponential functions were fitted to each treatment arm based on goodness of fit. Based on historical PBAC guidance (2006), trastuzumab's effect was assumed to be null after 5 years.

Component	Summary (March 2025 resubmission)
	Treatment effect A time limited treatment effect was included by applying the treatment effect to 7 years, followed by linear convergence to iDFS HR=1 (null effect) by year 10. The choice of 10 years was based on the HERA (n=5,102) and BCIRG-006 (n=3,222) trials. Remission A sustained remission adjustment was applied from the median follow-up (patients who achieved sustained remission) of the KATHERINE trial, increasing to 95% at 10 years.
Health related quality of life	The KATHERINE trial was used to estimate utilities for the iDFS, locoregional recurrence, and remission health states. Lloyd (2006) was used to estimate utilities for metastatic recurrence. iDFS on treatment = 0.786, iDFS off treatment = 0.799, locoregional recurrence = 0.786, remission 0.799, 1st line mBC = 0.753, 2nd line mBC = 0.481. The model assumed that patients experiencing locoregional recurrence would have the same utility as patients in iDFS on treatment and patients in remission would have the same utility as patients in iDFS off treatment. The type of systematic therapies used at different treatment phases could impact utilities and the QALY due to varying toxicity and adverse events. Nonetheless, the assumption was consistent with previous submissions for pertuzumab in eBC and was considered by the PBAC to be reasonable (Table 9, para. 6.31, pertuzumab PSD, July 2018 PBAC meeting and Table 10, para. 6.27, pertuzumab PSD, March 2019 PBAC meeting).
Costs	Pertuzumab (1 × 420mg vial) = $[redacted] (proposed AEMP for eBC). Pertuzumab (1 × 420mg vial) = $[redacted] (published AEMP for mBC). T-DM1 = $4,058.25 (published) Trastuzumab 1st cycle = $464.72 (AEMP) Trastuzumab 2-14 cycles = $414.20 (AEMP) The resubmission estimated that a neoadjuvant course of pertuzumab was expected to consist of 4.45 cycles of the drug for a total of 5.45 vials (420 mg) due to a loading dose of 840 mg in the first cycle. Cost data of neoadjuvant medicines, adjuvant medicines, medical services, post-progression therapies was from MBS and PBS. The assumptions regarding the utilisation of T-DM1 ([redacted]%) and T-DXd ([redacted]%) in mBC setting were uncertain. The cost per hospitalisation and adverse event costs were based on AR-DRGs from the NHCDC National Cost Weights for AR-DRG v10.0 - Round 23 (2018-19). An updated NHCDC National Cost Weights for AR-DRG v11.0 - (2020-21) was available.

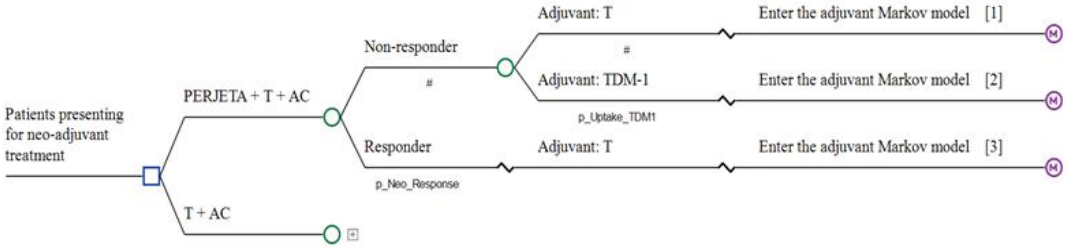
Source: Table 3-1, p144 of the resubmission, Section 3.4.1, p57 of the resubmission and Section 3.6.1, p174 of the resubmission.
ABS= Australian Bureau of Statistics; AEMP= approved ex-manufacturer price; AR-DRG= Australian refined diagnosis-related group; eBC= early breast cancer; HER2= human epidermal growth factor receptor 2; HR = hazard ratio; ICER= incremental cost-effectiveness ratio; iDFS= invasive disease free survival; LY= life years; mBC= metastatic breast cancer; MBS= Medicare Benefits Schedule; mg= milligram; m= number of patients; NHCDC= National Hospital Cost Data Collection; OS= overall survival; PBS= Pharmaceutical Benefits Scheme; pCR= pathological complete response; PFS= progression-free survival; P+T= pertuzumab + trastuzumab; P+T+Chemo = pertuzumab + trastuzumab + chemotherapy; T= trastuzumab; T+Chemo = trastuzumab + chemotherapy; T-DM1= trastuzumab emtansine; T-DXd= trastuzumab deruxtecan; QALY= quality adjusted life year.

6.53 The structure of the model for this resubmission comprised of 2 phases corresponding to the neoadjuvant and adjuvant settings. The model compared a neoadjuvant regimen that contained pertuzumab with one that did not. The economic model assumed that patients who did not have tpCR following neoadjuvant treatment received T-DM1 or trastuzumab in the adjuvant phase, while patients who responded to neoadjuvant treatment received trastuzumab only in the adjuvant phase. The

improved pCR achieved using neoadjuvant P+T+Chemo was translated into reduced utilisation and cost of adjuvant T-DM1, and resulted in an improvement in iDFS and ultimately to an improvement in life years and quality-adjusted life-years (QALYs).

6.54 The model structure and many of the inputs for this resubmission were based on the economic model accepted by the PBAC for T-DM1 (Table 10, trastuzumab emtansine PSD, November 2019 PBAC meeting), with an additional decision tree to reflect neoadjuvant treatment attached to the front (Figure 4).

Figure 4: Structure of the neoadjuvant phase of the economic model in this resubmission



Source: Figure 3-1, p142 of the resubmission.
AC=anthracycline; T=trastuzumab; T-DM1=trastuzumab emtansine.
[1] Patient enters the adjuvant phase of the model as a neoadjuvant non-responder, who receives adjuvant trastuzumab and accrues the costs and outcomes of adjuvant trastuzumab accordingly.
[2] Patient enters the adjuvant phase of the model as a neoadjuvant non-responder, who receives adjuvant T-DM1 and accrues the costs and outcomes of adjuvant T-DM1 accordingly.
[3] Patient enters the adjuvant phase of the model as a neoadjuvant responder, who receives adjuvant trastuzumab and accrues the costs and outcomes of a neoadjuvant responder accordingly.

6.55 The resubmission utilised response rate data combined with an assumed [redacted]% uptake rate for T-DM1 to estimate neoadjuvant treatment response and determine adjuvant treatment allocation into Markov models 1, 2 and 3 shown in Figure 4. The assumption regarding the uptake of T-DM1 was uncertain. However, the ICER was not sensitive to the uptake rate of T-DM1. Assuming an uptake rate of 100% reduced the ICER from $25,000 to < $35,000 to $15,000 to < $25,000 per QALY gained.

6.56 The resubmission did not directly apply the clinical evidence in the economic model, however the economic model used:

- The rate of neoadjuvant response (pCR) from a meta-analysis of neoadjuvant regimens containing anthracycline chemotherapy (consisting of 14 observational studies and the I-SPY2 trial) (**Error! Reference source not found.**). Using the NEOSPHERE trial pCR rate (P+T+ Chemo= 39.3% and T+ Chemo= 21.5%) reduced the incremental cost-effectiveness ratio (ICER) from $25,000 to < $35,000 (base case) to $15,000 to < $25,000/QALY gained. The ICER was not sensitive to the source of response rates, however the pre-PBAC response noted that it was sensitive to the difference in response rate compared to T+Chemo.
- The hazard ratio from Swain (2022) (HR= 0.35) to estimate disease recurrence for participants achieving pCR following neoadjuvant treatment. Swain (2022) pooled pCR and EFS data from the NEOSPHERE, TRYPHAENA, BERENICE, HannaH, and KRISTINE trials. This was reasonable; however, it introduced uncertainty (see para. 6.23). The

ICER was sensitive to the hazard ratio. Increasing the hazard ratio to 0.46 [Swain (2022) upper 95% CI] increased the ICER from $25,000 to < $35,000 (base case) to $45,000 to < $55,000/QALY gained. Furthermore, using HR= 0.54 from the NEOSPHERE trial (Table 9) increased the ICER from $25,000 to < $35,000 to $95,000 to < $115,000 ([redacted]% increase) per QALY gained. The Pre-Sub-Committee Response (PSCR) noted that sensitivity of the model to this value was reasonable given that the reduced risk of disease recurrence is the only benefit from achieving pCR included in the model, which does not capture other goals of neoadjuvant therapy (improving tumour resectability and the feasibility of breast-conserving surgery, decreasing surgical morbidity and extent of surgery, and allowing individualised adjuvant therapy options). The pre-PBAC response also noted that use of HRs from the upper 95% CI from Swain (2022) and from NEOSPHERE represent the most pessimistic case (the lowest likely surrogacy relationship).

6.57 Extrapolation of iDFS was conducted in 3 stages: first, parametric extrapolation of Kaplan-Meier data observed in the KATHERINE trial, then application of a time limited treatment effect to iDFS, and finally, application of a sustained remission adjustment (cure fraction) for a proportion of patients remaining in the iDFS health state.

6.58 The resubmission extrapolated the treatment effect to 7 years, with linear convergence to an iDFS HR of 1 (treatment effect null) over 3 years (until Year 10). The choice of 10 years was based on the HERA (n=5,102) and the BCIRG-006 (n=3,222) trials. The assumptions regarding treatment effects were uncertain, but they had minimal impact on the ICER.

6.59 The resubmission also applied a sustained remission adjustment (cure fraction) from the median follow-up of the KATHERINE trial (42 months or 3.5 years), increasing to 95% at 10 years. The resubmission stated this correction was made to the economic model to account for the time-limited effect of a treatment. However, this correction led to unrealistic survival curves that didn't match the observed patterns in clinical trials. The issue stems from the model's incorrect assumption of a constant or increasing risk of recurrence while the actual risk decreases over time for patients on the treatment.

6.60 The PBAC previously considered a sustained remission adjustment in the T-DM1 submission (Table 11, para. 6.30, trastuzumab emtansine PSD, November 2019 PBAC meeting). While the rationale for the adjustment in the recurrence rate was reasonable, the adjustment applied was uncertain. The resubmission did not present data to support the assumption that the change in the recurrence rate over time for patients treated with T-DM1 or pertuzumab was at least as low (if not lower) as that observed with trastuzumab. The ESC noted that the sustained remission rate of 95% was consistent with the T-DM1 model, and recalled it previously considered it was reasonable to assume some degree of sustained remission, though 95% was optimistic (para 6.35 trastuzumab emtansine PSD, November 2019 PBAC meeting). The sustained remission effect was a key driver of the ICER. Reducing the maximum

proportion of patients achieving sustained remission to 50% from 95% reduced the ICER/QALY gained to $5,000 to < $15,000 from $25,000 to < $35,000 (base case).

6.61 The model distributed iDFS events as either a distant recurrence or a locoregional/contralateral recurrence to inform health state destinations upon the recurrence event. The distributions for the neoadjuvant non-responders were based on the KATHERINE trial for the patients treated with T-DM1 and trastuzumab. The resubmission assumed that the distribution for neoadjuvant responders would be the same as for T-DM1 treated participants in the KATHERINE trial. This was reasonable.

6.62 The resubmission subdivided both mBC health states into early and late recurrence to more accurately model the disease course of mBC. The evaluation considered this was reasonable. The economic model used trastuzumab deruxtecan (T-DXd), in both the first-line mBC setting for patients with an early distant recurrence or in the second-line mBC setting. The resubmission assumed an uptake rate of [redacted]% for T-DXd in each eligible population, and the other [redacted]% will be treated with T-DM1. The ICER was not sensitive to the uptake rate. Hazard ratios of 0.28 and 0.55 were applied to the transition probabilities between 1st line mBC to 2nd line mBC (early recurrence) and 2nd line mBC to death for patients receiving T-DXd, based on data from the DESTINY Breast DB03 (DB03 trial from here on) trial. The ESC previously noted that there were significant transitivity issues between the Hamilton (2015), EMILIA and CLEOPATRA trials and the proposed T-DM1 population (para.6.33, trastuzumab emtansine, PSD, November 2019 PBAC meeting). The same would apply to the DB03 trial. It was unclear how these transitivity issues affected the ICER.

6.63 The resubmission used utility data from the KATHERINE trial, comparing iDFS on/off treatment for P+T+Chemo and T+Chemo in the adjuvant setting, most representative of the neoadjuvant setting. The resubmission distinguished between time on/off treatment to account for potential differences in health-related quality of life (HRQoL) associated with treatment use. The evaluation considered this was reasonable. No utility data were collected in the NEOSPHERE trial. The utility values were not a key driver of the ICER.

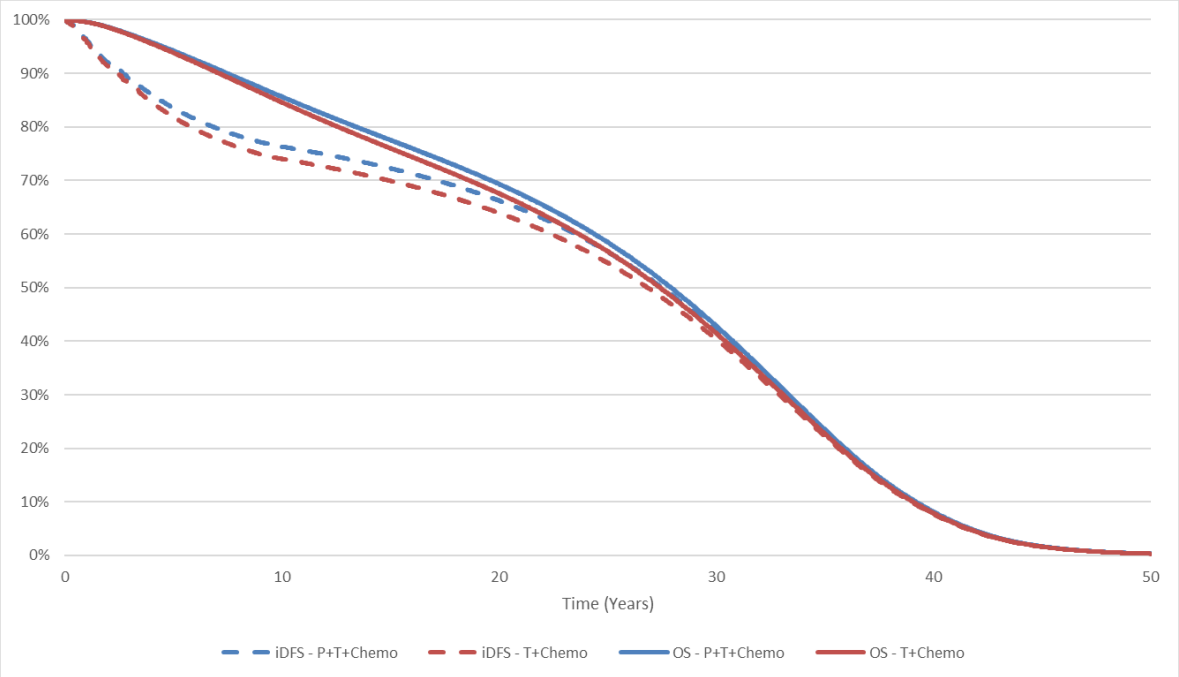
6.64 The resubmission estimated that a neoadjuvant course of pertuzumab was expected to consist of 4.45 cycles of the drug for a total of 5.45 vials (420 mg) due to a loading dose of 840 mg in the first cycle. The PSCR argued that 4.45 cycles of neoadjuvant pertuzumab is consistent with the clinical evidence presented for the submission and represents the mean treatment duration expected in clinical practice. Conversely, a duration of six cycles represents the maximum possible treatment duration and is not representative of the treated cohort as a whole. The ESC noted the number of cycles in the resubmission was based on the weighted average duration of treatment in a mix of trials that allowed either 4 or 6 cycles of neoadjuvant pertuzumab, and considered it was not necessarily representative of clinical practice. The proposed PBS indication was for neoadjuvant treatment with pertuzumab in combination with trastuzumab and chemotherapy, up to a maximum of 6 cycles (18 weeks) of therapy. The ICER was sensitive to the number of neoadjuvant cycles. Increasing the number

of cycles from 4.45 to 6 (based on the proposed PBS restriction) increased the ICER from $25,000 to < $35,000 to $45,000 to < $55,000/QALY gained ([redacted]% increase). The ESC noted that the model was sensitive to this input and considered information from the existing pertuzumab access program may be informative. The ESC noted it was unclear how the number of cycles of treatment may impact on the proportion of patients with pCR but noted that the model was not sensitive to the response rate applied. The pre-PBAC response noted that the model was not sensitive to the source of response rate, but was sensitive to the absolute level of response applied in the pertuzumab arm of the model and the difference in the response rate between arms. When the number of cycles increases to [redacted] as per the extent of use in the access program, without any change in the underlying response rate, the ICER increased from $25,000 to < $35,000 to $35,000 to < $45,000/QALY. However, the pre-PBAC response noted that if the response rate was then allowed to increase with this increase in treatment exposure it only needs to increase 2.8 percentage points (to 62.0% from 59.2%; 4.7% in relative terms) for the model result to return to an ICER of $25,000 to < $35,000. A reduction in the pertuzumab price of [redacted]% was required for an ICER of $15,000 to < $25,000 per QALY when the model assumed the cost for [redacted] cycles of treatment.

6.65 The resubmission applied a 40-year time horizon. The evaluation considered the proposed 40-year time horizon was relatively long, given the mean age of patients at the start of the economic evaluation was 58.5 years. The average life expectancy of Australian women aged 58 years in 2023 was 86.9 years (AIHW, 2023). The model estimated approximately 9% of patients remained alive and free of progressive disease at 98.5 years of age. This assumption may be optimistic as according to the Australian Life Tables 2020-22, only 6.3% of (all Australian) women are expected to reach the age of 99. The PBAC previously considered the 40-year time horizon used in the T-DM1 submission's base case to be inappropriate, as the median age at diagnosis with HER2+ early breast cancer (eBC) for women in Australia is 58.5 years and considered that greater confidence in establishing cost-effectiveness would be derived by limiting the time horizon to 20 years (para. 7.12, trastuzumab emtansine, PSD, November 2019 PBAC meeting). The ICER was sensitive to the time horizon, but only when the time horizon was shorter than 20 years. The ICER increased from $25,000 to < $35,000 to $35,000 to < $45,000/QALY gained when the time horizon was decreased from 40 years to 20 years. The ESC considered a time horizon of 30 years would be more appropriate given the mean age of patients at the start of the economic evaluation and the uncertainty in the longer term modelled outcomes.

6.66 Figure 5 presents modelled iDFS and OS for patients treated with neoadjuvant P+T+Chemo and T+Chemo over 50 years. This figure was generated during the evaluation using the Markov traces of neoadjuvant response rates for P+T+Chemo and T+Chemo (59.2% and 41.8%, respectively), and uptake of adjuvant T-DM1 for neoadjuvant non-responders.

Figure 5: Modelled iDFS and overall survival for patients treated with neoadjuvant P+T+Chemo and T-Chemo



Source: Generated during the evaluation using survival traces for neoadjuvant responders, neoadjuvant non-responders receiving T-DM1 and trastuzumab, neoadjuvant response rates for P+T+Chemo and T+Chemo (59.2% and 41.8%, respectively), and uptake of adjuvant T-DM1 for neoadjuvant non-responders from the economic model.
iDFS= invasive disease-free survival; OS= overall survival; P+T+Chemo=pertuzumab + trastuzumab + chemotherapy; T+Chemo=trastuzumab + chemotherapy; T-DM1= trastuzumab emtansine.

6.67 Overall, the Markov traces for T-DM1 and trastuzumab appeared reasonable. The model traces applied observed Kaplan-Meier iDFS data for the first 41.2 months. The modelled iDFS for 10 years was validated through comparison with the observed DFS from the HERA trial. The resubmission conducted no other validation of model traces.

6.68 At the 40-year time horizon, the neoadjuvant responder arm demonstrated a progression-free survival rate of 8.8%. For the non-responder arm, this rate was 6% for trastuzumab and 7.6% for T-DM1 receiving patients.

6.69 A summary of the key drivers of the model is shown in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Relative risk of disease recurrence	For neoadjuvant responders, an HR of 0.35 (Swain 2022) was applied to the trastuzumab arm of the KATHERINE trial.	High, favours P+T+Chemo ICER [redacted][2]/QALY gained by applying an HR = 0.46 (upper 95% CI). Using HR= 0.54 from the NEOSPHERE trial increased the ICER from [redacted][1] to [redacted][3]/QALY gained.
Time horizon	The resubmission applied a 40-year time horizon.	High, favours P+T+Chemo ICER = [redacted][4]/QALY gained assuming 20-year time horizon.
Number of neoadjuvant pertuzumab cycles	The resubmission estimated that a neoadjuvant course of pertuzumab was expected to consist of 4.45 cycles of the drug. The proposed PBS indication was up to a maximum of 6 cycles (18 weeks) of therapy.	High, favours P+T+Chemo ICER: 6 cycles was [redacted][2]/QALY gained.
Sustained remission adjustment	Adjustment to reflect the chance of achieving a sustained remission increasing over time, set to a maximum of 95% ten years after treatment initiation based on the HERA and BCIRG-006 trial evidence. Patients who achieved sustained remission are no longer at risk for a recurrence event and only experience risk of death as specified by the background mortality.	High, favours T+Chemo for all values less than 95% ICER: No sustained remission adjustment [redacted][5]/QALY gained.

Source: Table 3-1, p144 of the resubmission; Table 3-4, p152 of the resubmission; Table 3-5, p155 of the resubmission, and Section 3.2.2, pp149-152 of the resubmission,

CI = confidence interval; eBC= early breast cancer; EFS= event free survival; HER2= human epidermal growth factor receptor 2; HR= hazard ratio; ICER= incremental cost effectiveness ratio; iDFS= invasive disease free survival; mBC= metastatic breast cancer; PBS= Pharmaceutical Benefits Scheme; pCR= pathological complete response; RCT= randomised control trial; T-DM1= trastuzumab emtansine; P+T+Chemo = pertuzumab + trastuzumab + chemotherapy; QALYs= quality adjusted life years.

[a] The resubmission did not provide a reference for IPSOS (2018).

[b] Upper 95% confidence limit (HR=0.46) of the Swain (2022) point estimate.

The redacted values correspond to the following ranges:

[1] $25,000 to < $35,000

[2] $45,000 to < $55,000

[3] $95,000 to < $115,000

[4] $35,000 to < $45,000

[5] $0 to < $5,000

6.70 Key drivers of the March 2020 pertuzumab submission economic model were observed PFS benefit, parametric extrapolation of PFS, duration of treatment for mBC, costs in mBC and incorrect trastuzumab cost calculation (Table 13, para 6.45, pertuzumab PSD, March 2020 PBAC meeting).

6.36 Table 15 presents the results of the stepped economic evaluation. The resubmission only provided incremental costs and outcomes. Treatment-specific costs were estimated during the evaluation.

Table 15: Abbreviated results of the stepped economic evaluation

Step and component	P+T+Chemo	T+Chemo	Increment
Step 1: trial-based costs and outcomes (Pertuzumab costs only) – neoadjuvant time horizon			
Costs	$[redacted]	$[redacted]	$[redacted]
Outcome (pCR)	*59.2%*	*41.8%*	[redacted]%
Incremental cost/extra pCR (18 weeks)			[redacted][1]
Step 2: Translate response to reduction in disease recurrence – neoadjuvant time horizon + 1 year			
Costs[a]	$[redacted]	$[redacted]	$[redacted]
Outcome (iDFS years)	0.9923	0.9881	0.0041
Incremental cost/extra year in iDFS gained			[redacted][2]
Step 3: Incorporation of cost and effect of T-DM1 ([redacted]% T-DM1 use) – neoadjuvant time horizon + 1 year			
Costs	$[redacted]	$[redacted]	$[redacted]
Outcome (iDFS years)	0.9990	0.9977	0.0013
Incremental cost/extra year in iDFS gained			[redacted][2]
Step 4: Incorporation of all other costs – neoadjuvant time horizon + 1 year			
Costs	$[redacted]	$[redacted]	$[redacted]
Outcome (iDFS years)	0.9990	0.9977	0.0013
Incremental cost/extra year in iDFS gained			[redacted][2]
Step 5: Transform reduction in disease recurrence to life years – neoadjuvant time horizon + 1 year			
Costs	$[redacted]	$[redacted]	$[redacted]
Outcome (LYG)	1.3857	1.3857	0.00003
Incremental cost/extra LYG gained			[redacted][2]
Step 5a: Extend time horizon to 40 years			
Costs	$[redacted]	$[redacted]	$[redacted]
Outcome (LYG)	14.1756	14.0058	0.1698
Incremental cost/extra LYG gained			[redacted][3]
Step 6: Incremental cost/extra QALY gained (base case) – neoadjuvant time horizon + 40 years			
Cost	$[redacted]	$[redacted]	$[redacted]
Outcome (QALYs)	11.143	10.991	0.1520
Incremental cost/extra QALY gained (base case)			[redacted][4]
Incremental cost/extra QALY gained (base case) – 40-year time horizon (March 2020 submission)			
Costs	$[redacted]	$[redacted]	$[redacted][5]
Outcome (QALYs)	11.956	11.369	0.588
Incremental cost/extra QALY gained (base case)			[redacted][6]

Source: Table 3-25, pp189-190 of the resubmission; sheet 'NEOADJUVANT – Inputs and Result' of the Section 3 workbook; Table 3.21, p119 of the March 2020 submission. Values updated during the evaluation to include costs and outcomes for each treatment arm; splitting Step 5 into 5 and 5a to highlight the impact of the time horizon)

iDFS= invasive disease-free survival; LYG= life years gained; NR= not reported; pCR= Pathological complete response; P+T+Chemo = pertuzumab + trastuzumab + chemotherapy; T-DM1= trastuzumab emtansine. T-DXd= trastuzumab deruxtecan; T+Chemo = trastuzumab + chemotherapy; QALYs= Quality adjusted life years.

[a] The resubmission only presented the cost of pertuzumab in this step, However, the combined cost of neoadjuvant and adjuvant treatment was presented in sheet 'NEOADJUVANT – Inputs and Result' of the Section 3 workbook.

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

[2] *> $1,055,000*

[3] *$15,000 to < $25,000*

[4] *$25,000 to < $35,000*

[5] *$0 to < $5,000*

[6] *$5,000 to < $15,000*

6.71 These results were based on the sponsor's assumed price of T-DXd in the economic model ([redacted]% of the published price).

6.72 A comparison was also conducted during the evaluation, which explored which health state was driving the clinical benefit derived from the model. Time spent in the iDFS state was the key driver of the clinical benefit in the model (Table 16).

6.73 Table 16 presents the disaggregated QALYs from the economic evaluation. The proportion of total incremental QALYs gained at the neoadjuvant phase was -2.8%, and in the adjuvant phase and mBC setting was 102.8%.

Table 16: Disaggregated outcomes

Item	P+T+Chemo	T+Chemo	Incremental	% of total incremental (QALYs)
Time in neoadjuvant	0.345	0.345	0	
Time in iDFS (years)	12.799	12.492	0.307	-
Time in locoregional recurrence (years)	0.028	0.033	-0.0047	-
Time in remission (years)	0.182	0.212	-0.030	-
Time in distant recurrence (years)	0.371	0.416	-0.045	-
Time in 2nd line mBC (years)	0.451	0.509	-0.058	-
Life Years	**14.175**	**14.001**	**0.169**	**-**
QALYs				
QALYs in neoadjuvant	0.264	0.268	-0.004	-2.8%
QALYs in adjuvant and mBC	10.878	10.722	0.156	102.8%
QALYs	**11.143**	**10.991**	**0.152**	**100%**

Source: 3-27, p192 of the resubmission.
iDFS= invasive disease free survival; mBC= metastatic breast cancer; P+T+Chemo = pertuzumab + trastuzumab + chemotherapy; T+Chemo = trastuzumab + chemotherapy; QALYs= quality adjusted life years.

6.74 Table 17 presents the disaggregated costs from the economic evaluation.

Table 17: Disaggregated costs

Item	P+T+Chemo ($)	T+Chemo ($)	Incremental	% of total incremental (cost)
Neoadjuvant costs			$	%
Neoadjuvant AE costs			$	%
Adjuvant drug costs			-$	- %
Other adjuvant costs			-$	- %
Subsequent treatment costs			-$	- %
End of life costs			-$	%
Total			**$**	**%**

Source: Table 3-26, p191 of the resubmission. Italic values were calculated during the evaluation.
AE= adverse events; P+T+Chemo = pertuzumab + trastuzumab + chemotherapy; T+Chemo = trastuzumab + chemotherapy.

6.75 The cost of neoadjuvant pertuzumab ($) was offset by reduced use of treatments in the adjuvant setting ($) and subsequent settings ($). The cost savings from the reduction in adjuvant drug use were contingent on the response rate at the neoadjuvant treatment phase.

6.76 The results of key univariate and multivariate sensitivity analyses are summarised in Table 18.

Table 18: Results of univariate and multivariate sensitivity analyses

Analyses	Incremental cost ($)	Incremental QALY	ICER	% change to ICER
Base case	[redacted]	**0.152**	[redacted]	[redacted]
Time horizon (base case *40* years)				
20 years	[redacted]	0.096	[redacted]	[redacted]
30 years	[redacted]	0.139	[redacted]	[redacted]
Discount rate (base case: [redacted]%)				
[redacted]%	[redacted]	0.3823	[redacted]	[redacted]
[redacted]%	[redacted]	0.1962	[redacted]	[redacted]
Number of neoadjuvant pertuzumab cycles (4.45- base case)				
4 cycles	[redacted]	0.152	[redacted]	[redacted]
6 cycles	[redacted]	0.152	[redacted]	[redacted]
Relative risk of disease recurrence (HR=0.35 -base case)				
0.27 (95% LCL, Swain 2022)	[redacted]	0.194	[redacted]	[redacted]
0.49 (95% UCL, Swain 2022)[a] 0.46	[redacted]	0.082 0.097	[redacted]	[redacted]
0.54[b] (NEOSPHERE trial)	[redacted]	0.058	[redacted]	[redacted]
Neoadjuvant pCR rate(P+T+Chemo: 59.2%; T+Chemo: 41.8%) (Base case)				
NEOSPHERE tpCR (P+T+Chemo: 39.3%: T+Chemo: 21.5%)	[redacted]	0.1556	[redacted]	[redacted]
Sustained remission adjustment (Yes- base case-95%) No 50%	[redacted]	0.280 0.229	[redacted]	[redacted]
Pooled proportion of distant and locoregional recurrence (Selected button 'arm specific': T-DM1 arm- base case) Pooled	[redacted]	0.136	[redacted]	[redacted]
Utility weights for eBC				
eBC utility Selection (KATHERINE Pooled-base case) Hedden et al. 2012	[redacted]	0.108	[redacted]	[redacted]
mBC utility Selection (Lloyd et al. 2006-base case) Rautalin et al. 2017 Lidgren et al. 2007	[redacted]	0.142 0.133	[redacted]	[redacted]

Analyses	Incremental cost ($)	Incremental QALY	ICER	% change to ICER
Multivariate analysis				
20-year time horizon and 6 treatment cycles per patient	[redacted]	0.096	[redacted][9]	[redacted]%
20-year time horizon; treatment cycle 6/per patient and relative risk of disease recurrence in patients with a pCR (HR=0.46)		0.058	[redacted]	[redacted]%
Multivariate analysis - ESC				
30-year time horizon; treatment cycle 6/per patient	[redacted]	0.139	[redacted][5]	[redacted]%
30-year time horizon and relative risk of disease recurrence in patients with a pCR (HR=0.46)		0.088	[redacted][6]	[redacted]%
30-year time horizon; treatment cycle 6/per patient and relative risk of disease recurrence in patients with a pCR (HR=0.46)		0.088	[redacted][7]	[redacted]%
30-year time horizon; treatment cycle 6/per patient and relative risk of disease recurrence in patients with a pCR (HR=0.46); sustained remission reduced to 50%		0.1377	[redacted][5]	[redacted]%

Source: Table 3-29, pp194-195 of the resubmission and compiled during evaluation.
ICER= incremental cost effectiveness ratio; HR= hazard ratio; LCL= lower confidence interval; pCR= Pathological complete response; T= trastuzumab; T-DM1= trastuzumab emtansine; QALYs= quality adjusted life years; UCL = upper confidence interval.
[a] The resubmission used 0.49 as the upper 95% CI, however 0.49 was the upper 95% CI for the comparison between P+T+Chemo in the neoadjuvant and adjuvant setting versus T+Chemo in the neoadjuvant and adjuvant setting, regardless of pCR status.
[b] Value reported in Table 2-23, p85 of the resubmission.
The redacted values correspond to the following ranges:
[1] *$25,000 to < $35,000*
[2] *$35,000 to < $45,000*
[3] *$5,000 to < $15,000*
[4] *$15,000 to < $25,000*
[5] *$45,000 to < $55,000*
[6] *$55,000 to < $75,000*
[7] *$95,000 to < $115,000*
[8] *$0 to < $5,000*
[9] *$75,000 to < $95,000*
[10] *$135,000 to < $155,000*

6.77 The ICER was most sensitive to the time horizon (40 years vs 20 years) ([redacted]% increase in ICER), number of neoadjuvant treatment cycles (4.45 cycles vs 6 cycles) ([redacted]% increase in ICER), and hazard ratio [Swain (2022) HR= 0.35 vs HR=0.46] for disease recurrence ([redacted]% increase in ICER). Reducing the maximum proportion of patients achieving sustained remission to 50% from 95% reduced the ICER/QALY gained by [redacted]%.

6.78 A multivariate sensitivity analysis with a 20-year time horizon, 6 treatment cycles per patient, and the relative risk of disease recurrence in patients achieving a pCR (HR = 0.46, upper CI from Swain (2022)) resulted in the ICER increasing from $25,000 to < $35,000 to $135,000 to < $155,000/QALY gained. The PSCR considered this multivariate sensitivity analysis was of questionable use for decision-making purposes, arguing that none of the three parameters tested could be considered the most reasonable or reliable estimates of the available evidence (a 20-year time horizon is

substantially lower than the population's life expectancy; treatment costs based on 6 cycles reflect the maximum possible treatment cost but does not reflect the evidence used in the model; and the upper 95% CI from Swain represents the lowest likely benefit of achieving a response in the neoadjuvant setting).

6.79 The ESC noted that a multivariate analysis with a 30-year time horizon and a hazard ratio of disease recurrence in patients achieving pCR (HR = 0.46, upper 95% CI from Swain (2022)), resulted in the ICER increasing from $25,000 to < $35,000 to 55,000 to < $75,000. A multivariate sensitivity analysis with a 30-year time horizon, 6 treatment cycles per patient, and a hazard ratio of disease recurrence in patients achieving pCR (HR = 0.46, upper 95% CI from Swain (2022)), resulted in the ICER increasing from $25,000 to < $35,000 to $95,000 to < $115,000/QALY gained.

Drug cost/patient/course

6.80 The cost per patient per course of neoadjuvant treatment with pertuzumab is presented in Table 19. The proposed treatment involved adding pertuzumab to T+Chemo. The resubmission assumed that the T+Chemo component of the treatment regimen would be unchanged and, since it was common to the intervention and comparator arm, was not costed (for economic model and financial estimates). This was reasonable. Only the additional cost of pertuzumab is presented in Table 19, the mean dose and duration of the comparator, and the cost per patient/course of T+Chemo are not presented.

Table 19: Drug cost per patient for pertuzumab as neoadjuvant treatment – proposed effective price

	Trial dose and duration (NEOSPHERE)	Economic model	Financial estimates
Mean dose	Cycle 1: 840mg Cycles 2-4: 420mg		
Mean duration	3.9 cycles	4.45 cycles	4.45 cycles
Cost/patient/cycle[a]	Cycle 1: $[redacted] Cycles 2+: $[redacted]	Cycle 1: $[redacted] Cycles 2+: $[redacted]	Cycle 1: $[redacted][c] Cycles 2+: $[redacted]
Cost/patient/course	$[redacted]	$[redacted][b]	$[redacted][c]

Source: Table 3-15, p176 of the resubmission.
mg= milligram; yr = year.
[a] Based on proposed effective AEMP of $[redacted] for one 420 mg vial and public/private hospital utilisation of 18.59%:81.41%
[b] Modelled estimate did not round to 4.45 cycles. Verifying using a calculator produced an estimate of $[redacted].
[c] revising the Cycle 1 calculation to be (2*AEMP for one 420 mg vial) + EFC markups for public and private hospitals changed the cost of Cycle 1 to $[redacted] and the cost/patient/course to $[redacted], consistent with the economic model.

6.81 The cost (DPMA) in the first cycle was calculated correctly in the economic model but incorrectly in the financial estimates in the submission. This was corrected during the evaluation as in Table 21. The cost of subsequent cycles was calculated consistently in the economic model and financial estimates as AEMP+EFC markups.

6.82 The cost/patient/course based on the NEOSPHERE trial was lower than the cost estimated in the economic model and financial estimates. The NEOSPHERE trial had a mean duration of 3.9 cycles, whereas the economic model and financial estimates applied a mean duration of 4.45 cycles based on the I-SPY2 trial and 5 observational

studies where P+T+Chemo included anthracyclines and the number of neoadjuvant cycles was reported (Acevedo 2023, Bilici 2023, Canino 2024, Hung 2022, and Vieira 2023 from Table 4). The ESC noted that DUSC previously considered the estimate of 4 cycles per patient was an overestimate and considered 3.7 would be a reasonable estimate (based on the duration of treatment in the NEOSPHERE trial). However the ESC noted that this did not reflect recommendations for neoadjuvant pertuzumab in the Australian PI (6 cycles) or current ESMO guidelines (6-8 cycles). The ESC considered information from the existing pertuzumab access program may be informative to verify or revise this input in both the economic model and financial estimates. The sponsor provided information regarding the duration of neoadjuvant pertuzumab treatment and the duration of adjuvant pertuzumab treatment for Australian patients in its pre-PBAC response, which indicated that on average patients were treated for [redacted] cycles of neoadjuvant pertuzumab (see also paragraph 6.92).

Estimated PBS usage & financial implications

6.83 This submission was not considered by DUSC. The resubmission took an epidemiological approach to estimate the number of patients treated with neoadjuvant pertuzumab. The resubmission claimed that it did not differ greatly from the March 2020 submission in that trastuzumab is used to estimate the eligible patient population given pertuzumab will be used as an "add-on" treatment to trastuzumab. This was reasonable. However, the approach was different to the March 2020 submission that used a modified market share approach based on trastuzumab PBS script substitution. The DUSC considered the approach taken in the March 2020 submission to be reasonable (para. 6.59, pertuzumab PSD, March 2020 PBAC meeting).

6.84 The resubmission performed the following steps to estimate the total number of pertuzumab vials per year:

- Estimated the number of patients potentially eligible for pertuzumab based on PBS 10% data.
- Estimated the proportion of patients receiving neoadjuvant treatment.
- Estimated the rates of uptake of pertuzumab.
- Estimated the number of vials of pertuzumab per patient per year.

6.85 Table 20 presents the key inputs relied on in the financial estimates.

Table 20: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Number patients potentially eligible for pertuzumab	Yr 1: [redacted]1 Yr 2: [redacted]1 Yr 3: [redacted]1 Yr 4: [redacted]1 Yr 5: [redacted]1 Yr 6: [redacted]1	PBS 10% sample, eBC patients initiating treatment with trastuzumab 2006-2024. Exponential function based on moving 5-year average: y=1,160.5e^0.0343x, where y = number of patients and x = difference in years from initial year (2006).	The evaluation considered this was reasonable.
Proportion of patients receiving neoadjuvant treatment	80%	Duffield (2023) and market research data.	The evaluation considered this was reasonable. However, data from Duffield (2023) used an uncertain long-term exponential extrapolation.
Treatment utilisation			
Uptake rate	Yr 1: [redacted]%, increasing to Yr 6: [redacted]%	Submission estimate.	Uptake was expected to be high due to the superior effectiveness of pertuzumab plus trastuzumab relative to current standard of care. This was uncertain.
Number of vials of pertuzumab per patient	5.45	Estimated based on the weighted average duration of treatment in studies included in the resubmission.	This was consistent with the economic model. Sensitivity analysis was conducted assuming 6 vials per patient. See also paragraph 6.82.
P+T+Chemo response rate	59.2%	Estimated from the meta-analysis of studies including anthracyclines	The evaluation considered this was reasonable. This affected the downstream use of T-DM1 and trastuzumab in the adjuvant setting, and treatment in mBC.
T+Chemo response rate	41.8%	Estimated from the meta-analysis of studies including anthracyclines	
Uptake of adjuvant T-DM1 in neoadjuvant non-responders	[redacted]%	Assumed	This was uncertain but consistent with the economic model.
Costs			
Pertuzumab (DPMA; public, private)	<u>Published</u> Initial (2 vials): $3,008.88, $3,094.41 Continuing (1 vial): $3,008.88, $3,094.41 <u>Effective</u> Initial (2 vials): $[redacted], $[redacted] Continuing (1 vial): $[redacted], $[redacted]	<u>Proposed AEMP</u> Published: $[redacted] Effective: $[redacted] The resubmission presented the number of vials rather than the number of scripts and stated that although 2 vials are taken in the initiating stages (one script), it was assumed these were separate scripts in the Workbook. The DPMAs were calculated as (AEMP for one 420 mg vial) + EFC markups instead of (2*AEMP for one 420 mg vial) + EFC markups.	The initial DPMAs should be: Published: $5,927.63, $6,054.03; Effective: $[redacted], $[redacted]. The financial impact using corrected DPMAs is presented in Table 21.

Data	Value	Source	Comment
Adjuvant T-DM1 (DPMA)	Public: $7,270.12 Private: $7,415.30	PBS items 11951B & 11956G	
Adjuvant trastuzumab (DPMA)	Public: $708.44 Private: $731.70	PBS Items 4703M & 7267L	
Reduction in metastatic treatment costs (cumulative per patient)	Yr 1: -$[redacted] Yr 2: -$[redacted] Yr 3: -$[redacted] Yr 4: -$[redacted] Yr 5: -$[redacted] Yr 6: -$[redacted]	Output from the economic model	The evaluation considered this was reasonable. The economic model included the cost of treating locoregional recurrence.
MBS costs	None	None	This was inconsistent with the economic model, which included changes in MBS utilisation (e.g. intravenous drug administration).

Source: Tables 4-6, 4-7, 4-9, 4-11, 4-13 & 4-15of the resubmission.
Chemo=chemotherapy; DPMA=dispensed price for maximum amount; P=pertuzumab; PBS=Pharmaceuticals Benefit Scheme; T=trastuzumab; T-DM1=Trastuzumab emtansine; Yr=year.
The redacted values correspond to the following ranges:
[1] 500 to < 5,000

6.86 In addition to changing from a market share to epidemiological approach, key differences between the March 2020 submission and the resubmission included the uptake rate of neoadjuvant treatment (was 27-52%, now 80%), uptake rate of pertuzumab (was 60-80%, now [redacted]-[redacted]%), and number of neoadjuvant cycles (was 4, now 4.45). The resubmission also included cost offsets for adjuvant and metastatic treatment.

6.87 The method used to estimate the cost offsets for T-DM1 and trastuzumab in the adjuvant setting double counted the EFC dispensing fees. The PSCR provided revised financial estimates correcting the pertuzumab DPMA and revising the cost offsets in the adjuvant setting to remove the double counting of EFC dispensing fees.

6.88 Table 21 presents the estimated use and financial implications to the PBS/RPBS of listing pertuzumab using the effective prices of pertuzumab and assumed effective price of T-DXd ([redacted]% reduction from published price).

Table 21: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated with pertuzumab	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of pertuzumab vials per patient per year	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total pertuzumab scripts[a,b]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications of pertuzumab						
Cost to PBS/RPBS less copayments	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Cost to PBS/RPBS less copayments PSCR revised	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments: adjuvant treatment	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Cost to PBS/RPBS less copayments: adjuvant treatment PSCR revised	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Cost to PBS/RPBS less copayments: metastatic treatment	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Net financial implications						
Net cost to PBS/RPBS[a,c,d]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Net cost to PBS/RPBS PSCR revised	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net cost to PBS/RPBS PSCR revised assuming 6 cycles pertuzumab	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Revisions as proposed by PBAC						
Net cost to PBS/RPBS assuming [redacted] cycles neoadjuvant pertuzumab	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net cost to PBS/RPBS assuming [redacted] cycles neoadjuvant pertuzumab + 3% patients adjuvant pertuzumab, mean 13.0 cycles	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
As above, [redacted]% price reduction for neoadjuvant scripts, [redacted]% price reduction for adjuvant scripts	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]

Source: Table 4-7, p204, Table 4-10, p206, Table 4-15, p210 and Table 4-18, p213 of the resubmission; Table 4.9, p139 of the March 2020 submission; Table 1, pertuzumab, DUSC Advice, March 2020 PBAC meeting.

PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme, MBS = Medicare Benefits Schedule.

[a] Initial pack size adjusted from 1 to 2 to reflect 2 vials provided with initial script (change made to cell K117 of sheet 3a. Scripts – proposed of the Section 4 workbook).

[b] Each patient is estimated to use 1 initial script and 3.45 continuing scripts (4.45 cycles of neoadjuvant treatment).

[c] initial DPMAs revised to $[redacted] (public) and $[redacted] (private) (change made to cells H274 and I274 of sheet 3c. Impact – proposed (eff).

[d] Co-payments adjusted to reflect 2024 values (changes made to cells I78:N78 of sheet 2e. Scripts – market).

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *5,000 to < 10,000*

[3] *10,000 to < 20,000*

[4] *$20 million to < $30 million*

[5] *net cost saving*

[6] *$0 to < $10 million*

[7] $10 million to < $20 million

6.89 The total cost to the PBS/RPBS of listing pertuzumab was estimated in the resubmission to be $0 to < $10 million in Year 1 and $0 to < $10 million in Year 6, and a total of $50 million to < $60 million in the first 6 years of listing. The corrections in the PSCR financial estimates resulted in an increase in the total cost to the PBS/RPBS of listing pertuzumab to $10 million to < $20 million in Year 1 and $0 to < $10 million in Year 6, and a total of $60 million to < $70 million in the first 6 years of listing.

6.90 Compared to the previous submission, the cost for pertuzumab was higher $100 million to < $200 million over 6 years in this resubmission vs $100 million to < $200 million over 6 years in the previous resubmission (Table 1, DUSC report for March 2020 PBAC meeting) but the overall net cost was lower ($$50 million to < $60 million vs. $70 million to < $80 million) due to the inclusion of cost offsets for adjuvant and metastatic treatment $80 million to < $90 million over 6 years in this resubmission vs $20 million to < $30 million over 6 years in the previous resubmission).

6.91 The net cost to the PBS/RPBS was moderately sensitive to the proportion of patients receiving neoadjuvant treatment, the uptake of pertuzumab and the number of vials of pertuzumab per patient per year. It was also sensitive to the response rates. Use of the I-SPY2 response rates (55.6% for P+T+Chemo and 25.8% for T+Chemo, Clark (2021)) resulted in a higher incremental difference in response rate and additional cost offsets from adjuvant T-DM1.

6.92 The ESC noted that the number of treatment cycles of pertuzumab likely to be used in clinical practice was uncertain (see also paragraphs 6.64 and 6.82). The PBAC noted that additional data from the patient access program provided with the pre-PBAC response, indicated that on average, patients received [redacted] cycles of pertuzumab in the neoadjuvant setting. The pre-PBAC noted that these data will overestimate the average number of cycles in clinical practice because they exclude any patients who discontinued treatment after only one cycle. In addition, patients were required to pay out of pocket for the first cycle and therefore may have been more motivated to complete their course than what might be expected in the general PBS population. The PBAC considered that the impact of these factors on the mean duration is unknown but likely to be minimal, and considered that [redacted] cycles is a reasonable estimate of the number of neoadjuvant treatment cycles in clinical practice. Increasing the duration of treatment to [redacted] cycles increased the net cost to the PBS/RPBS $80 million to < $90 million over the first 6 years of listing.

6.93 The evaluation noted there is the potential for usage outside the proposed PBS restriction for pertuzumab in patients with low risk eBC and as adjuvant treatment for eBC. However, the ESC noted that treatment guidelines specify use in patients with high risk eBC and considered that use in the low risk population would be contrary to both guidelines and the PBS listing (as proposed). The PSCR also noted that clinician feedback suggests a preference for low risk eBC patients (i.e. node-negative and cancer of less than 2cm) to receive surgical treatment, and noted the primary goals of neoadjuvant treatment, such as tumour or nodal downstaging, are not as relevant in

low-risk eBC patients. Additionally, the commentary noted that the TGA PI recommends "Patients who start Perjeta and trastuzumab in the neoadjuvant setting, should continue to receive adjuvant Perjeta and trastuzumab to complete one year of treatment (maximum 18 cycles)". The PSCR stated that the continued use of pertuzumab in the adjuvant setting was unlikely, as reflected in the sponsor's pertuzumab Adjuvant Patient Access Program, which has 20 patients, compared to the widespread utilisation of pertuzumab in the Neoadjuvant Patient Access Program. The access program data for patients treated with pertuzumab over the period June 2019 to June 2024, provided in the pre-PBAC response, indicated that around 1% of patients (27/2,670) continued to receive adjuvant pertuzumab following neoadjuvant pertuzumab.

6.94 The PBAC noted that over the period June 2019 to June 2024, 77 patients received adjuvant pertuzumab through the access program in the adjuvant setting only (without prior neoadjuvant pertuzumab). The mean duration of treatment for these patients was 13.0 cycles when capped at a maximum duration of 18 cycles (12 months treatment). The PBAC considered that few patients would receive primary surgery (approximately 10%), and fewer still (approximately 2-3% in total) would be considered high risk following primary surgery and therefore eligible for pertuzumab. This was consistent with the small number of patients treated via the access program (77/2,747, <3%). When the financial estimates were adjusted to include an additional 3% of eBC patients receiving adjuvant only treatment (with uptake assumed to be the same as in the neoadjuvant setting, and with a treatment duration of 13.0 cycles) the financial estimates increased to 90,000 to < 100,000 over the first 6 years of listing.

6.95 When the AEMP for pertuzumab was reduced by [redacted]% (neoadjuvant setting) and [redacted]% (adjuvant setting), the estimated net cost to the PBS/RPBS decreased to 70,000 to < 80,000 over the first 6 years of listing.

Quality Use of Medicines

6.96 The resubmission did not comment on any quality use of medicines issues. With the complexity in the management of eBC, education for prescribers and patients is required, including discussion of the role of treatment with pertuzumab, in terms of outcomes and adverse effects to inform decision-making.

Financial Management – Risk Sharing Arrangements

6.97 The resubmission did not propose any risk sharing arrangements for pertuzumab.

6.98 In the March 2020 submission, the ESC noted that there were caps in place for T-DM1 and pertuzumab in the metastatic setting (para. 6.68, pertuzumab PSD, March 2020 PBAC meeting). The cost-effectiveness analysis assumed cost offsets for reduced use of T-DM1 and pertuzumab in the mBC setting due to fewer patients progressing to metastatic disease (para. 6.68, pertuzumab PSD, March 2020 PBAC meeting). To ensure the modelled cost-offsets were realised, the ESC considered that it may be appropriate to reduce the T-DM1 and pertuzumab expenditure caps in the mBC setting in line with the assumptions and outputs from the economic model for

subsequent treatments (para. 6.68, pertuzumab PSD, March 2020 PBAC meeting). The ESC previously 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 (para. 6.69, pertuzumab PSD, March 2020 PBAC meeting).

6.99 The PBAC noted that the expected changes to pertuzumab and T-DM1 utilisation in the metastatic setting are expected to be small relative to the total costs. The PBAC considered that the expected change to the utilisation of T-DM1 in the adjuvant setting was substantial and the cost-effectiveness of pertuzumab was reliant on cost offsets for adjuvant T-DM1. The PBAC considered that the RSA caps for T-DM1 should be revised to account for the expected reduction in utilisation associated with an increased number of patients with pCR following neoadjuvant pertuzumab, although acknowledged that the actual reduction in PBS expenditure for T-DM1 will be lower than estimated given that a substantial number of patients are already accessing pertuzumab via the patient access program.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of pertuzumab for the neoadjuvant treatment of human epidermal growth factor receptor 2 positive (HER2+) high risk early breast cancer, on the basis that it should be available only under special arrangements under Section 100. The PBAC considered that the resubmission appropriately addressed its previous concerns regarding the clinical place for pertuzumab, and the incremental benefit from adding pertuzumab in the neoadjuvant setting was adequately supported by the evidence, which demonstrated that increasing the proportion of patients with pathological complete response is associated with improved PFS and OS. The PBAC considered that adjuvant treatment with pertuzumab would also be appropriate for a proportion of patients, consistent with international guidelines and the Australian Product Information (PI) for pertuzumab. The PBAC considered that the cost-effectiveness for pertuzumab would be acceptable with a price reduction and risk sharing arrangements that ensured that the cost of treatment in the adjuvant setting was contained to the patient population where there is evidence of treatment benefit.

7.2 The PBAC is satisfied that the addition of pertuzumab to trastuzumab and chemotherapy (P+T+Chemo) provides, for some patients, a significant improvement in efficacy over trastuzumab and chemotherapy alone.

7.3 The PBAC considered that the appropriate clinical place for pertuzumab has become clearer since the Committee's previous considerations of its use in the neoadjuvant and adjuvant settings. The PBAC noted the need for equitable access to neoadjuvant pertuzumab, which has become the standard of care in international guidelines, and is currently privately funded for many patients. The PBAC also considered that there

is a need for subsidised access to adjuvant pertuzumab for the subset of patients most likely to benefit from it, particularly the small number of patients who receive primary surgery (without neoadjuvant treatment), noting that the Australian PI and international guidelines include adjuvant pertuzumab as an option for patients at high risk of recurrence.

7.4 The PBAC noted the nominated comparator for P+T+Chemo was trastuzumab + chemotherapy (T+Chemo). The PBAC noted that the resubmission appropriately addressed its previous concern regarding the comparator by accounting for the availability and efficacy of T-DM1 as adjuvant treatment for patients with residual disease following surgery (para 7.2, pertuzumab PSD, March 2020 PBAC meeting). The PBAC noted that the resubmission presented additional evidence to support the surrogacy of pCR for survival endpoints (PFS or DFS) and to address its previous concern regarding inclusion of anthracycline-based regimens as the neoadjuvant chemotherapy (para7.12 pertuzumab PSD, March 2020 PBAC meeting).

7.5 The PBAC considered that the proposed clinical criteria for the restrictions appropriately limited treatment to patients with HER2+ high risk breast cancer, and agreed with the ESC that it would be preferable to include “high risk” for clarity (see paragraph 3.5). The PBAC also considered it was reasonable to not specify the type of chemotherapy in the restriction. The PBAC considered that it would be preferable for the restrictions to allow treatment in the adjuvant setting, to address equity issues, and for consistency with the Australian PI and international guidelines. The PBAC considered that to allow adjuvant pertuzumab treatment, the proposed restriction criteria regarding surgery should be removed and the proposed restrictions regarding the maximum duration of treatment should be amended to specify a total of 12 months of treatment including both initial and continuing restrictions (18 3-weekly cycles).

7.6 The PBAC noted that the primary evidence included in the submission was based on three head-to-head RCTs comparing four cycles of P+T+Chemo to T+Chemo as neoadjuvant treatment for eBC (NEOSPHERE, PEONY and I-SPY2). In addition, the submission presented evidence from TRYPHAENA, which provided outcomes using six neoadjuvant cycles of P+T+Chemo, including anthracycline-based or carboplatin-based neoadjuvant chemotherapy regimens. The PBAC noted that none of the studies were powered for survival outcomes and key outcomes of the trial were pCR. The PBAC noted that in the 3 RCTs more than 17% additional patients had pCR in the trial arms treated with neoadjuvant pertuzumab (added to T+chemo) compared with the T+Chemo arms. In PEONY and NEOSPHERE more than 39% of patients treated with P+T+Chemo had a pCR, and in TRYPHAENA more than 56% of patients in both arms had pCR. The PBAC considered that the evidence supported the claim that the addition of neoadjuvant pertuzumab to T+Chemo increases the rate of pCR.

7.7 The PBAC noted that the submission presented evidence from Swain (2022) to support the surrogacy of pCR to the patient relevant outcome of EFS. Swain et al analysed the relationship between neoadjuvant pCR and EFS in 5 RCTs of pertuzumab, trastuzumab

(or both) in the neoadjuvant and adjuvant settings (NEOSPHERE, TRYPHAENA, BERENICE, HannaH, and KRISTINE trials). The PBAC noted Swain (2022) found that participants with pCR had decreased risk of an EFS event versus those with residual disease (HR: 0.35, 95% CI: 0.27-0.46). The PBAC noted that based on the results from NEOSPHERE alone the relationship for the risk of a EFS/DFS event in patients with pCR vs residual disease was not as strong (HR: 0.54, 95% CI: 0.29-1.00). However, the PBAC acknowledged that NEOSPHERE was a relatively small study and therefore less reliable than the meta-analysis from Swain (2022). The PBAC noted that other trials not specific to pertuzumab also supported pCR as a surrogate endpoint for EFS, though the HRs reported were slightly less favourable than in Swain (2022). Overall the PBAC considered the evidence supported the claim that pCR is likely to be associated with a decreased risk of disease recurrence and improved survival outcomes, however noted that the quantification of the surrogate relationship was somewhat uncertain and may be less favourable than the HR from Swain (2022), which was used as the basis for the economic evaluation.

7.8 The PBAC noted that additional supportive evidence demonstrating the efficacy of pertuzumab in addition to chemotherapy regimens containing an anthracycline was presented. The resubmission identified 14 observational studies comparing P+T+Chemo to T+Chemo where the neoadjuvant chemotherapy backbone included anthracyclines. The difference in pCR rate between P+T+Chemo and T+Chemo among the observational studies involving a range of chemotherapies was similar to that in the NEOSPHERE and PEONY trials where docetaxel was administered. The PBAC noted the limitations of the observational studies but considered the additional data presented helped to address its previous concern regarding the effectiveness of pertuzumab when used with anthracyclines.

7.9 The PBAC considered the claim of inferior safety of Ptz+T+Chemo compared with T+Chemo was reasonable, noting the substantial increase in left ventricular systolic dysfunction in NEOSPHERE (8.4% vs 1.9% of patients), and the substantial 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 noted that the submission did not provide evidence for use of pertuzumab as adjuvant treatment as the submission request was for neoadjuvant treatment only. However, the PBAC recalled that it had previously considered evidence from the APHINITY trial, an RCT comparing P+T+Chemo vs T+Chemo, which showed the iDFS event-free rates for node-positive patients were 89.88% vs. 86.68% at 4 years (difference of 3.2%), respectively. The PBAC noted that updated results of 8-year iDFS in the node-positive cohort showed an absolute improvement of 4.9% favouring pertuzumab (86.1% vs. 81.2%; HR: 0.72, 95% CI: 0.60-0.87]). The PBAC noted that the APHINITY trial did not include patients treated in the neoadjuvant setting, and therefore the outcomes are only directly relevant to patients initially considered node negative, or who elect to not undergo neoadjuvant treatment prior to surgery. The PBAC noted that the PEONY trial provided very limited evidence for adjuvant

treatment with P+T following neoadjuvant P+T+Chemo as it was a small trial with limited applicability and the extent of benefit from pertuzumab treatment in the adjuvant setting was unclear as patients in the control arm did not receive neoadjuvant pertuzumab. However, the Australian PI recommends patients who start P+T+Chemo in the neoadjuvant setting should continue to receive adjuvant P+T to complete one year of treatment, and international guidelines include adjuvant pertuzumab as a treatment option for lymph node positive patients who have pCR following surgery.

7.11 The PBAC noted the resubmission presented a cost-effectiveness analysis comparing P+T+Chemo versus T+Chemo in the neoadjuvant setting for patients with HER2-positive high-risk eBC. The economic evaluation was changed from the March 2020 submission and was largely based on the economic model presented for T-DM1 (November 2019 submission) as an adjuvant treatment for patients with eBC and residual disease. The economic model assumed that patients who did not have pCR following neoadjuvant treatment received T-DM1 or trastuzumab in the adjuvant phase, while patients who responded to neoadjuvant treatment received trastuzumab only in the adjuvant phase. The PBAC noted that the model was driven by the increase in pCR when using neoadjuvant P+T+Chemo which resulted in reduced utilisation and cost of adjuvant T-DM1, and an improvement in iDFS, life years and QALYs. The PBAC considered that the revised approach to the model in the resubmission was appropriate.

7.12 The PBAC noted that the model used a time horizon of 40 years, which it considered was too long, given the mean age of patients at the start of the economic evaluation was 58.5 years. However, the PBAC noted that the model was not sensitive to use of a 30 year time horizon, which it considered was more reasonable. The PBAC noted that the main areas of uncertainty in the economic model were the relative risk of recurrence and the estimated number of neoadjuvant cycles of pertuzumab, both of which had a substantial impact on the ICER. The PBAC considered that the HR for disease recurrence from Swain (2022) was uncertain and may be optimistic, however acknowledged it was the most directly relevant data source to inform this input. The PBAC noted that the sponsor provided information regarding the duration of pertuzumab treatment from the patient access program, as requested by the ESC. The PBAC noted that this indicated that, on average, patients received [redacted] cycles of neoadjuvant pertuzumab. Increasing the number of neoadjuvant pertuzumab cycles to [redacted], without any change in the underlying response rate, the ICER increased from $25,000 to < $35,000 to $35,000 to < $45,000 per QALY. The pre-PBAC response argued that the number of cycles in the base case (4.45) reflected the duration of treatment associated with the response rate observed in the clinical evidence as applied in the model. The sponsor argued that if the response rate was increased with the increase in treatment exposure it would need to increase from 59.2% to 62.0% for the model result to return to an ICER less than $25,000 to < $35,000 per QALY. The PBAC considered that there was no evidentiary basis to support a 2.8% absolute

increase in response rate with additional cycles, and noted that a reduction in price of [redacted]% was required for an ICER of $15,000 to < $25,000 per QALY when the model assumed the cost for [redacted] cycles of treatment. The PBAC considered that neoadjuvant pertuzumab would be cost-effective at a reduced price to result in an ICER of $15,000 to < $25,000/QALY or less.

7.13 The PBAC noted that the economic model presented was not structured to assess the cost-effectiveness of adjuvant pertuzumab. The PBAC recalled that 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 PSD, March 2019 PBAC meeting). The PBAC considered that there was now greater clarity regarding the clinical place for adjuvant treatment with pertuzumab in patients with high risk eBC, however the cost-effective price remained uncertain. The PBAC considered that at the price proposed in the March 2019 submission (AEMP $[redacted], a [redacted]% reduction compared to the price proposed in the neoadjuvant setting) adjuvant pertuzumab treatment may be considered cost-effective for the small number of patients with high risk eBC who were initially considered node negative, or who elect not to undergo neoadjuvant treatment prior to surgery (approximately 2-3% of eBC patients); noting that this patient population was represented in the APHINITY trial. The PBAC considered that for lymph node positive patients who start P+T+Chemo in the neoadjuvant setting and have pCR following surgery, adjuvant pertuzumab is a treatment option according to guidelines, however the evidence supporting this use is limited and its cost-effectiveness is unknown. In order to address the equity of access issue for patients currently self-funding adjuvant pertuzumab, the PBAC considered that it would be reasonable to include the option of adjuvant treatment for this population if the additional cost to Government could be minimised via implementation of an RSA.

7.14 Overall, the PBAC considered that PBS listing of pertuzumab, for a maximum total treatment duration of 12 months in the neoadjuvant or adjuvant setting, would be acceptably cost-effective with a weighted reduction in price of [redacted]% for neoadjuvant scripts and [redacted]% for adjuvant scripts and RSA financial caps based on 1) the neoadjuvant population and 2) the small number of patients with high risk eBC who were initially considered low risk/node negative, or who elect not to undergo neoadjuvant treatment prior to surgery. The PBAC considered that adjuvant treatment with pertuzumab following neoadjuvant pertuzumab may be clinically appropriate for some patients, however its cost-effectiveness has not been established, and these patients should not be included in financial estimates informing RSA financial caps. The PBAC considered that a rebate of close to 100% would be appropriate for utilisation above the financial caps.

7.15 The PBAC noted the submission's approach to estimating the incident population for neoadjuvant treatment with pertuzumab relied on use of the 10% PBS data sample and considered that the approach was reasonable for estimation of patient numbers. The PBAC considered that a duration of [redacted] cycles should be applied, consistent with the economic model. The PBAC also considered it would be reasonable to increase the financial estimates to include the 3% of patients for whom adjuvant treatment with pertuzumab may be appropriate (high risk eBC, initially considered low risk/node negative, or who elect not to undergo neoadjuvant treatment prior to surgery). For these patients, the PBAC considered the financial estimates should apply a mean duration of 13.0 cycles, based on data from the patient access program. The PBAC noted that with a [redacted]% reduction in the AEMP price for neoadjuvant pertuzumab (from $[redacted] to $[redacted] per vial) and [redacted]% reduction in the AEMP for adjuvant pertuzumab ($[redacted] per vial) the total cost to the PBS/RPBS of listing pertuzumab was estimated to be $10 million to < $20 million in Year 1 and $10 million to < $20 million in Year 6, and a total of $70 million to < $80 million in the first 6 years of listing. The PBAC considered these estimates were a reasonable basis for the proposed RSA financial caps.

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

a) The treatment is expected to provide a moderate, but clinically relevant improvement in efficacy;

b) The treatment is not expected to address a high and urgent unmet clinical need as other treatments are available in this setting;

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

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Secretariat suggested wording for the restriction

Suggested additions are in italics and deletions in strikethrough.

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
PERTUZUMAB Injection	NEW (Public) NEW (Private)	840 mg	0
Available brands			
Perjeta (pertuzumab 420 mg/14mL, 14 mL vial)			
Restriction Summary [new] / Treatment of Concept: [new]			
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: ☒Medical Practitioners		
	Restriction type: ☒Authority Required – immediate assessment (telephone/online)		
Prescribing Rule Level	**Administrative Advice:** No increase in the maximum amount or number of units may be authorised.		
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Indication: Early HER2 positive breast cancer		
	Treatment Phase: Initial treatment		
	Clinical criteria		
	Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by in situ hybridisation (ISH)		
	AND		
	Clinical criteria:		
	Patient must have locally advanced, inflammatory or early stage, high risk (tumour >2 cm in diameter or lymph node positive) breast cancer		
	AND		
	Clinical criteria:		
	The treatment must be in combination with trastuzumab		
	AND		
	Clinical criteria:		
	The treatment must be used in combination with trastuzumab		
	AND		
	Clinical criteria:		
	The treatment must be initiated in combination with chemotherapy		
	AND		
	Clinical criteria:		
	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		
	Clinical criteria:		
	Patient must not receive more than 1 treatment cycle under this restriction.		
	AND		
	Clinical Criteria		
	The treatment for initial and continuing therapy combined must not extend beyond either (i) 18 weeks (6 cycles) in the neoadjuvant setting; (ii) 12 months (18 cycles) in total		
	Prescribing Instructions: Details (date, unique identifying number/code, or provider number) of the pathology report from an Approved Pathology Authority confirming evidence of HER2 gene amplification by in situ hybridisation (ISH) must be provided at the time of application. The pathology report must be documented in the patient's medical records.		

	Prescribing Instructions: Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
PERTUZUMAB Injection	NEW (Public) NEW (Private)	420 mg	4

Available brands
Perjeta (pertuzumab 420 mg/14mL, 14 mL vial)

Restriction Summary [new] / Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required – immediate assessment (telephone/online)
Prescribing rule level		**Administrative Advice:** No increase in the maximum amount or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Indication: Early HER2 positive breast cancer
		Treatment Phase: Continuing treatment
		Clinical criteria
		Patient must have previously received PBS-subsidised treatment with this drug for this condition
		AND
		Clinical criteria:
		The treatment must be used in combination with trastuzumab
		AND
		Clinical criteria:
		The treatment must have been initiated in combination with chemotherapy
		AND
		Clinical criteria:
		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
		Clinical Criteria
		The treatment for initial and continuing therapy combined must not extend beyond either (i) 18 weeks (6 cycles) in the neoadjuvant setting; (ii) 12 months (18 cycles) in total
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

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

9 Context for Decision

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

10 Sponsor's Comment

Roche welcomes the PBAC's decision to recommend pertuzumab for the treatment of patients with HER2-positive high-risk early breast cancer and is working with the Department of Health towards a PBS listing.