

**6.07 TRASTUZUMAB EMTANSINE,
Powder for I.V. infusion 100 mg,
Powder for I.V. infusion 160 mg,
Kadcyla[®],
Roche Products Pty Ltd.**

1 Purpose of Application

- 1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing of trastuzumab emtansine (T-DM1) for adjuvant therapy of patients with human epidermal growth factor receptor 2 (HER2) positive early breast cancer (eBC) with residual disease following HER2-targeted neoadjuvant therapy that included trastuzumab and taxane-based chemotherapy. This is the first application to the PBAC for the use of T-DM1 in the adjuvant setting in eBC.
- 1.2 The submission presented a cost utility analysis comparing T-DM1 with trastuzumab. The key components of the clinical issue presented in the submission are summarised in Table 1.

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

Component	Description
Population	People with HER2+ eBC who have pathological residual disease in the breast and/or axillary lymph nodes following neoadjuvant therapy that included trastuzumab and taxane-based chemotherapy.
Intervention	T-DM1 3.6 mg/kg given IV every three weeks for 14 cycles
Comparator	Trastuzumab 8 mg/kg followed by 6 mg/kg given IV every three weeks for 14 cycles (an 8 mg/kg loading dose should be given in cases where there has been an interval greater than 6 weeks since the last dose of trastuzumab).
Outcomes	Primary: iDFS Secondary: iDFS-SPNBC, OS, DFS, DRFI, AEs and HRQoL.
Clinical claim	In people with HER2+ eBC, T-DM1 was more effective than trastuzumab at improving iDFS. In people with HER2+ eBC, T-DM1 is inferior in terms of safety compared with trastuzumab, but the AEs profile was established and manageable with minimal impact on HRQoL, maintaining a positive risk/benefit ratio.

Abbreviations: AEs= adverse events; DFS= disease free survival; DRFI= distant relapse-free interval; eBC= early breast cancer; HER2= human epidermal growth factor receptor 2; HRQoL= health-related Quality of Life (QoL); IV= intravenous; iDFS= invasive disease-free survival; iDFS-SPNBC= invasive disease-free survival including second primary non-breast cancers; kg= kilogram; mg= milligram; OS= overall survival; SC= subcutaneous; T-DM1= trastuzumab emtansine.

Source: Table 1.1, p.14 of the submission.

2 Requested listing

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

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TRASTUZUMAB EMTANSINE (T-DM1) Solution for IV infusion 100 mg in 5 mL (20 mg/mL) 160 mg in 8 mL (20 mg/mL)	450 mg	6	Public: \$7642.32 Private: \$7787.34	Kadcyla Roche Products Pty Ltd

Category/Program	Section 100 – Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required Public Hospital Authority Required
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity	Early
Condition:	HER2 positive early breast cancer [14765]
Indication:	Adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease after pre-operative systemic treatment that included HER2-targeted therapy Early HER2 positive breast cancer [7754]
Treatment phase:	Initial adjuvant treatment (3-weekly regimen)
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) in the primary tumour [new concept; 14665 modified] AND Patient must have evidence of residual invasive cancer, as demonstrated by a pathology report, in the breast and/or axillary lymph nodes following completion of surgery [new concept] AND Patient must have completed systemic neoadjuvant therapy that included trastuzumab and taxane-based chemotherapy prior to surgery [new concept] AND The treatment must be as monotherapy [7910]-The treatment must be the sole PBS-subsidised anti-HER-2 therapy [15452] AND The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure [7745] AND Patient must not receive more than 42 weeks (14 cycles) of combined PBS-subsidised and non-PBS-subsidised therapy with this drug under both the initial and continuing adjuvant treatment restrictions combined [new concept]

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<p>Administrative Advice Prescribing Instructions</p>	<p>Authority applications for initial treatment must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Early Breast Cancer - PBS Supporting Information Form which includes:</p> <p>(i) a copy of the pathology report from an approved pathology authority confirming the presence of HER2 gene amplification by in situ hybridisation (ISH); and</p> <p>(ii) a copy of the pathology report from an approved pathology authority demonstrating evidence of residual invasive carcinoma in the breast and/or axillary lymph nodes following completion of preoperative therapy</p> <p>(iii) a copy of the signed patient acknowledgement form. [new concept; 7750 modified; (iii) to be phased out]</p> <p>Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval and then at 3 monthly intervals during treatment. [18136]</p> <p>Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval. [24537]</p>
<p>Administrative advice</p>	<p><u>Note:</u></p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 [concept 7753; Complex Authority Required flag]</p>

<p>Category/Program</p>	<p>Section 100 – Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required Public Hospital Authority Required</p>
<p>Prescriber type:</p>	<p><input type="checkbox"/>Dental <input checked="" type="checkbox"/>Medical Practitioners <input type="checkbox"/>Nurse practitioners <input type="checkbox"/>Optometrists <input type="checkbox"/>Midwives</p>
<p>Severity</p>	<p>Early</p>
<p>Condition:</p>	<p>HER2 positive early breast cancer [14765]</p>
<p>Indication:</p>	<p>Adjuvant treatment of patients with HER2 positive early breast cancer who have residual disease after pre-operative systemic treatment that included HER2 targeted therapy Early HER2 positive breast cancer [7754]</p>
<p>Treatment phase:</p>	<p>Continuing <i>adjuvant</i> treatment (3 weekly regimen)</p>
<p>Restriction Level / Method:</p>	<p><input type="checkbox"/>Restricted benefit <input type="checkbox"/>Authority Required – In Writing <input checked="" type="checkbox"/>Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/>Streamlined</p>

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Clinical criteria:	<p>Patient must have previously been issued with an authority prescription for this drug for this condition [19469] AND The treatment must be as monotherapy [7910] The treatment must be the sole PBS-subsidised anti-HER-2 therapy [15452] AND The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure [7745] AND Patient must not receive more than 42 weeks (14 cycles) of combined PBS-subsidised and non-PBS-subsidised therapy with this drug under both the initial and continuing adjuvant treatment restrictions combined [new concept]</p>
Administrative Advice Prescribing instructions	<p>Authority applications for initial treatment must be made in writing and must include:- (a) a completed authority prescription form; and (b) a completed Early Breast Cancer – PBS Supporting Information Form which includes: (i) a copy of the pathology report from an approved pathology authority confirming the presence of HER2 gene amplification by in situ hybridisation (ISH); and (ii) a copy of the pathology report from an approved pathology authority demonstrating evidence of residual invasive carcinoma in the breast and/or axillary lymph nodes following completion of preoperative therapy (iii) a copy of the signed patient acknowledgement form. [new concept]</p> <p>Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval and then at 3 monthly intervals during treatment. [18136]</p>
Administrative Advice	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). [14726; Complex Authority Required flag]</p>

- 2.2 The submission proposed initial, continuing and grandfathered treatment criteria. No special pricing arrangement was proposed.
- 2.3 The submission proposed that in all settings, use of T-DM1 was restricted to not more than 42 weeks (14 cycles) of combined PBS-subsidised and non-PBS-subsidised therapy.
- 2.4 The proposed restriction is largely consistent with the use of T-DM1 in the KATHERINE trial (the main source of the evidence comparing T-DM1 with trastuzumab), the proposed TGA PI and Australian guidelines (Cancer Council 2016 and eviQ ID: 127 and ID: 1323). At its March 2019 meeting, the PBAC considered it would be appropriate for all trastuzumab listings, to be revised to encompass adjuvant and neoadjuvant treatment for eBC (Trastuzumab (Ogivri) Public Summary Document (PSD), March 2019, paragraph 5.4). The Economics Sub-Committee (ESC) noted that this recommendation was implemented on 1 October 2019 and the listings for trastuzumab in early HER2 positive breast cancer now include the clinical criterion “Patient must have undergone surgery (adjuvant) or be preparing for surgery (neoadjuvant)”.

- 2.5 The submission proposed that the continuing listing for T-DM1 should be Authority Required (STREAMLINED). The current listings for T-DM1 require a written authority application for initial treatment while a telephone authority application is permitted for continuing treatment. The PBAC considered that a written authority application for initial treatment and a telephone authority application for continuing treatment would be appropriate in order to limit treatment to 42 weeks (14 cycles), and given the much higher cost of treatment compared to trastuzumab.
- 2.6 The submission requested a separate grandfathering restriction for patients receiving T-DM1 prior to the commencement of PBS listed supply. The Secretariat noted that grandfathered patients would qualify for treatment under the initial treatment restriction and therefore a separate grandfathering listing would not be required. The PBAC considered it would be appropriate for grandfathered patients to access T-DM1, but that the initial treatment restriction should include criteria requiring that treatment with T-DM1 must be initiated within 12 weeks after surgery. The PBAC considered that it would be appropriate for patients initiated on T-DM1 to switch to trastuzumab if unable to tolerate T-DM1.
- 2.7 The submission stated that the proposed population should have their HER2 status tested by in situ hybridization (ISH) in the primary tumour. This aligns with evidence from the KATHERINE trial and current clinical practice where HER2 status is tested prior to neoadjuvant therapy commencing. The PBAC noted that patients would have established HER2 status prior to commencing neoadjuvant trastuzumab and therefore would not need to re-test to be eligible for T-DM1.
- 2.8 The PBAC considered that the wording of the restriction should be amended to remove the requirement that treatment be as monotherapy as many patients require concomitant use of endocrine therapy. This would align with current practice, the evidence from KATHERINE and the suggestion made in the TGA Clinical Evaluator's Report (CER). While the PBAC noted that an alternative option could be to include a clinical criterion stating that 'The treatment must be the sole PBS-subsidised anti-HER2 therapy', the PBAC considered this was not required as there are no other anti-HER2 therapies available on the PBS in this treatment setting.
- 2.9 The DUSC considered there is a low risk that T-DM1 will be used outside of the restriction, given the written Authority Required PBS listing.

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

3 Background

Registration status

- 3.1 The submission was made under TGA/PBAC Parallel Process. T-DM1 was first approved for registration by the Therapeutic Goods Administration (TGA) on 26th August 2013 for the treatment of patients with HER2+ metastatic breast cancer (mBC)

who previously received trastuzumab and a taxane, separately or in combination. The sponsor sought TGA approval for the use of T-DM1 as “adjuvant treatment of patients with HER2+ eBC who have residual disease after pre-operative systemic treatment that included HER2-targeted therapy”.

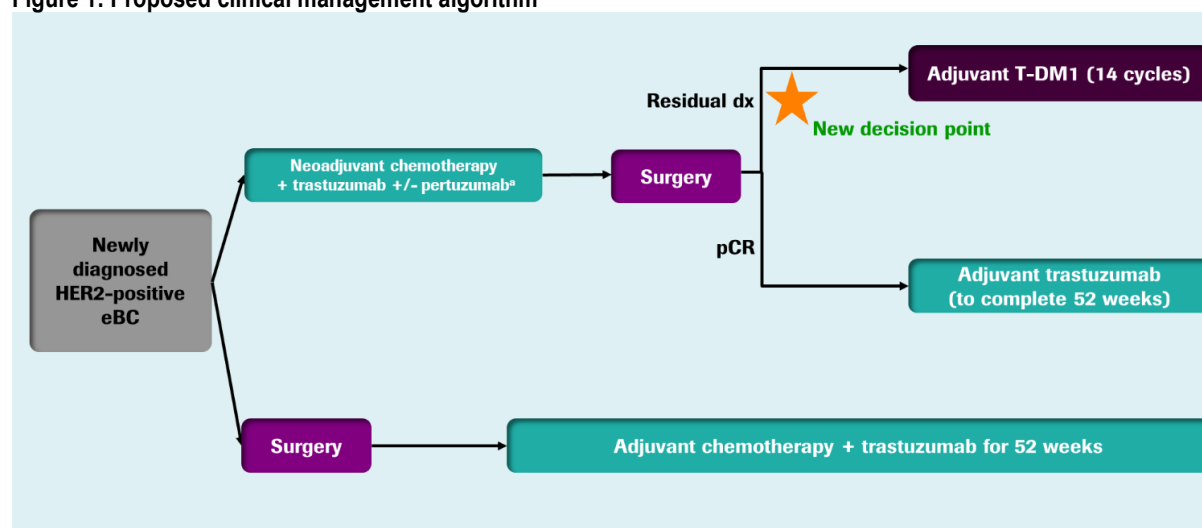
- 3.2 T-DM1 was approved by the TGA on 1 October 2019 for “[as a single agent], the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment”.
- 3.3 T-DM1 was approved by the FDA on 3rd May 2019 for the same indication as TGA. The ESC noted that the Pre-Sub-Committee-Response (PSCR) stated that the KATHERINE data have been submitted to the EMA with approval expected in November 2019.

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

4 Population and disease

- 4.1 Breast cancer (BC) is the most frequently diagnosed malignancy in women and the leading cause of cancer mortality in women worldwide. In Australia, 16,753 people were diagnosed with BC, and 2,868 died as a result of BC, in 2014 (AIHW 2017). HER2+ BC occurs when breast cells overexpress the HER2 receptor due to an oncogenic mutation in the HER2 gene. HER2+ tumours tend to grow faster than luminal cancers and are often associated with worse prognosis (Dai 2015). In Australia, approximately 15% of BC patients are HER2+ based on ISH testing (Bilous 2012a).
- 4.2 In Australia, operable eBC is defined as tumours not more than five centimetres in diameter, either impalpable or palpable, but not fixed lymph nodes and with no evidence of distant metastases (NBOCC 2008). Women with large operable or locally advanced tumours may require neoadjuvant therapy to reduce tumour bulk prior to surgery to improve surgical outcomes.
- 4.3 The PBS listing for T-DM1 proposed in this submission is as adjuvant treatment of patients with HER2+ eBC who have residual disease after pre-operative systemic treatment that included HER2-targeted therapy. This is a new approach for determining which adjuvant treatment patients should have, with the aim being to select those with a higher risk of recurrence. The submission’s proposed treatment algorithm is presented in Figure 1. The PBAC considered this to be appropriate.

Figure 1: Proposed clinical management algorithm



Abbreviations: dx=disease; eBC= early breast cancer; HER2= human epidermal growth factor receptor 2; pCR=pathological complete response.

Source: Figure 1.3, p. 25 of the submission

Note: Neoadjuvant therapy may be appropriate for locally advanced breast cancers as well as some larger operable breast cancers to down-stage tumours, either to make them operable or to allow breast-conserving therapy; a: neoadjuvant pertuzumab is currently available via the Roche patient access program.

- 4.4 The PBAC recently noted that there is a move towards neoadjuvant therapy in patients with high risk eBC. The PBAC also noted that a recent large meta-analysis of eBC trials with neoadjuvant chemotherapy¹ reported the prognostic importance of pathological complete response (pCR), which correlates with event free and overall survival (Neratinib PSD, March 2019, paragraph 4.5). The ESC noted that the trastuzumab PBS listing was updated on 1 October 2019 to allow trastuzumab and chemotherapy (T+Chemo) to be used as adjuvant or neoadjuvant treatment for HER2+ eBC (Trastuzumab Ogivri PSD, March 2019 para 5.4, p5).
- 4.5 The current and proposed clinical algorithms were inconsistent with the current PBS funded treatment pathway as pertuzumab is not PBS listed for neoadjuvant eBC treatment. Currently patients may only access dual HER2 therapy with pertuzumab in the neoadjuvant setting through self-funding, however the PSCR stated that the sponsor intends to seek PBS funding for pertuzumab in the neoadjuvant setting.
- 4.6 T-DM1 is a HER2-targeted antibody-drug conjugate containing the humanised anti-HER2 IgG1 antibody trastuzumab, covalently linked to the small molecule cytotoxin, DM1. The proposed dosing for T-DM1 is as an intravenous infusion (3.6 mg/kg) every 3 weeks to make up a total of 14 cycles (42 weeks) of therapy. This dosing schedule is

¹Spring L, et al: Pathological complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival, stratified by breast cancer subtypes and adjuvant chemotherapy usage. 2018 San Antonio Breast Cancer Symposium. Abstract GS2-03. Presented December 5, 2018.

consistent with that presented in KATHERINE, the proposed restriction and the most recent draft T-DM1 PI (Kadcyla PI 2019) and TGA-approved PI for trastuzumab (Herceptin PI, June 2019), though the trastuzumab PI also allows weekly IV infusions. The PI for trastuzumab SC injections (Herceptin SC PI, June 2019) contains different dosage regimens, however the PBAC previously accepted trastuzumab SC is non-inferior in efficacy and safety compared with trastuzumab IV (Trastuzumab SC PSD, July 2015, paragraph 7.7).

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

5 Comparator

- 5.1 The submission nominated trastuzumab as the main comparator on the basis that trastuzumab is the standard of care (SoC) for the adjuvant treatment of HER2+ eBC following neoadjuvant therapy. This is consistent with the current PBS listing in this patient population. At its March 2019 and July 2019 meetings, the PBAC recommended the listing of four biosimilars of trastuzumab, Ogivri and Ontruzant (March 2019) and Herzuma and Kanjinti (July 2019). Ogivri was listed on the PBS 1 August 2019 and Herzuma was listed on the PBS 1 November 2019; the other biosimilars are not yet PBS listed.
- 5.2 Trastuzumab is PBS listed for neoadjuvant and adjuvant treatment of eBC. It is also PBS listed for the treatment of mBC and treatment of advanced gastric cancer. Trastuzumab can be administered IV or SC. The TGA indication for trastuzumab in eBC is “for the treatment of HER2-positive early breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy”.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (6) and organisations (3) via the Consumer Comments facility on the PBS website. The comments were all supportive of T-DM1 as adjuvant treatment in eBC. The comments noted the significant improvement in disease-free survival for patients with HER2 positive eBC who have a poor response to neoadjuvant chemotherapy as demonstrated in the KATHERINE trial. The comments noted that the results would be expected to translate to improved overall survival with longer follow-up. The comments from health professionals noted that the KATHERINE trial established T-DM1 as a new standard of care for patients with this subtype of breast cancer [HER2-

positive, high risk of recurrence] which previously had a poor prognosis. The comments from health care professionals noted that T-DM1 is well established in the advanced breast cancer setting and its side effects are manageable.

- 6.3 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) clarifying the likely use of T-DM1 in clinical practice. The PBAC specifically noted the use of T-DM1 will provide patients who do not have a pCR following neoadjuvant treatment, with a new treatment option in this setting. The BCNA noted that T-DM1 is an effective treatment for people who may otherwise have a higher risk of developing metastatic disease. The BCNA noted the high financial cost of accessing T-DM1 privately and that listing it on the PBS would allow more equitable access to this effective therapy. The BCNA also noted that listing T-DM1 would have potential savings to the Australian health budget if fewer people go on to develop metastatic disease. The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.4 The Medical Oncology Group of Australia (MOGA) and its Breast Cancer Expert Group also expressed strong support for the T-DM1 submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of improved disease free survival in the KATHERINE trial, but noting that the OS benefit was immature. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for T-DM1, which was grade A (out of A, B and C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies)², based on a comparison with trastuzumab alone.

Clinical trials

- 6.5 The submission was based on one head-to-head randomised controlled trial (RCT), KATHERINE, comparing T-DM1 to trastuzumab. Details of the trial presented in the submission are provided in Table 2.

² Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
KATHERINE	A randomised, multicentre, open-label Phase III Study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2+ primary breast cancer who have residual tumour present pathologically in the breast or axillary lymph nodes following preoperative therapy.	KATHERINE CSR, Report No. 1087528, January 2019
	Main Report: (KATHERINE CSR 2019), Clinical Appendix. Clinical Study Report, Study BO27938, KATHERINE CSR, Report No. 1087528	NEJM 2019; 380(7):617-28.
	von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2+ Breast Cancer.	
	Schneeweiss A. Patient-reported outcomes (PROs) from KATHERINE: A phase III study of adjuvant trastuzumab emtansine (TDM1) versus trastuzumab (H) in patients (pts) with residual invasive disease after neoadjuvant therapy for HER2+ breast cancer.	ASCO Annual meeting. 2019; Poster session

Source: Table 2.4, p41 and p73 of the submission.

6.6 The key features of the direct randomised trial are summarised in Table 3 below. The ESC considered that the KATHERINE trial was a well-conducted trial with a low risk of bias and an appropriate sample size.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
T-DM1 vs. trastuzumab						
KATHERINE	1486	MC, OL, R, 42:52 weeks ^a (T-DM1: trastuzumab)	Low	Post-neoadjuvant therapy	iDFS, iDFS-SPNBC, DFS, OS, DRFI, HRQoL, AEs	iDFS, iDFS-SPNBC, DFS, OS, HRQoL, AE.

Abbreviations: DFS=disease-free survival; DRFI=distant recurrence-free interval; iDFS= invasive disease-free survival; HRQoL= health-related quality of life; MC=multi-centre; OL=open label; OS= overall survival; R=randomised; SPNBC= second primary non-breast cancer.

Source: Table 2.7 and Table 2.8, Table 3.6, 49-50 and p84 of the submission.

Note: a. duration of use until disease recurrence, unacceptable toxicity or max duration of 14 cycles (42 weeks) for T-DM1 or 52 weeks for trastuzumab.

6.7 The primary efficacy outcome for KATHERINE was iDFS; this is the preferred efficacy end point for eBC (stages I to IIIA) adjuvant trials (2007 STEEP Guidelines). The submission proposed a minimal clinically important difference (MCID) for iDFS using the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). When used to assess treatments with curative intent, an improvement in DFS alone measured with a hazard ratio (HR) with a lower limit 95% confidence interval between 0.65 and 0.8, is considered a clinical benefit that represents substantial improvement (Cherny 2015). The commentary considered this was appropriate.

6.8 The main differences between KATHERINE and the proposed population were the median age (49 vs. 58.5 years in the Australian population), the proportion receiving

dual targeted (most commonly, pertuzumab plus trastuzumab) neoadjuvant therapy (19.5% vs. 40% in the Australian population), neoadjuvant anthracyclines (77% vs. 37-57%) and adjuvant radiotherapy (83% vs. 36% in the Australian population). These differences may reduce the applicability of the results for T-DM1 to the Australian setting.

Comparative effectiveness

6.9 The primary outcome for the interim analysis was designated as the analysis of iDFS after 256 (67%) of the targeted 384 iDFS events had occurred and crossed the O’Brien-Fleming stopping boundary ($p < 0.0124$ or observed HR < 0.732).

6.10 The results from KATHERINE for iDFS are presented in Table 4, with the corresponding Kaplan-Meier data in Figure 2.

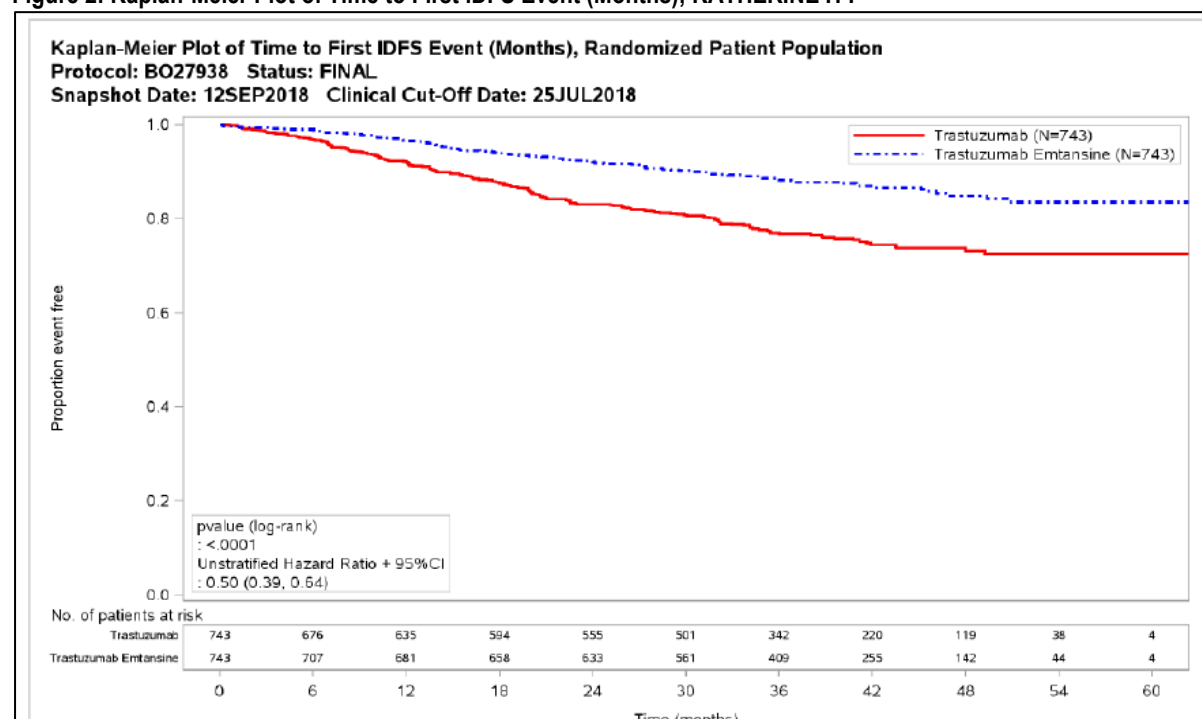
Table 4: Results of iDFS of KATHERINE

Population	T-DM1	Trastuzumab	RD* (%) (95% CI)	P value (log rank test)	Hazard ratio (95% CI)
	Patients with events, n (%)	Patients with events, n (%)			
ITT (25 July 2018)	91/743 (12.2%)	165/743 (22.2%)	-10.0 (-6.2, -13.8)	<0.0001	0.50 (0.39, 0.64)

Abbreviations: CI= confidence interval; iDFS= invasive disease-free survival; ITT= intent-to-treat; HR= hazard ratio; n= number of participants reporting data; N= total participants in group; NE= not evaluated; RD= risk difference; T-DM1= trastuzumab emtansine
Source: Table 2.9, p53 of the submission and calculated during evaluation.

Notes: *RD calculated during evaluation using RevMan version 5.3. **Bold** indicates statistically significant results.

Figure 2: Kaplan-Meier Plot of Time to First iDFS Event (Months); KATHERINE ITT



Abbreviations: CI= confidence intervals; iDFS= invasive disease-free survival; p= p value.

Source: Figure 2.3, p54 of the submission.

- 6.11 The submission noted that KATHERINE met its primary endpoint after a median follow-up of 41 months, demonstrating a statistically significant and clinically meaningful improvement in iDFS for T-DM1 compared to trastuzumab. Patients receiving T-DM1 had a 50% reduction in the risk of recurrence or death. The result for iDFS was statistically significant in favour of T-DM1 with HR=0.50 (95% CI: 0.39, 0.64; p<0.0001). The ESC considered that this reduction in iDFS was clinically meaningful but noted that it was based on a population with a relatively low baseline risk, albeit a higher risk subset of the eBC population.
- 6.12 For most patients with an iDFS event, distant recurrence occurred as the first event and occurred numerically more frequently in the trastuzumab arm (16.3% vs. 10.5%; Table 7). A breakdown of the iDFS events contributing to the primary endpoint is presented in Table 5. The ESC noted that a higher proportion of distant recurrences occurred in the CNS in the T-DM1 arm compared with the trastuzumab arm (48.4% vs 19.4%, respectively). However, the ESC noted that neither T-DM1 nor trastuzumab penetrate the blood brain barrier, therefore neither would be expected to prevent CNS recurrence. The ESC noted the difference in distribution of sites of recurrence (as shown in Table 6) suggests that T-DM1 reduced the number of metastases in other sites, including lung/liver metastases, compared with trastuzumab which it considered would be clinically significant.

Table 5: Summary of First Occurrence* of an iDFS Event: KATHERINE, ITT

	T-DM1 n/N (%) per event type N = 91	Trastuzumab n/N (%) per event type N = 165
Total patients with iDFS event	91 (100%)	165 (100%)
Distant recurrence – non-CNS	34 (37.4%)	86 (52.1%)
Distant recurrence – CNS	44 (48.4%)	32 (19.4%)
Loco-regional recurrence	8 (8.8%)	34 (20.6%)
Contralateral BC	3 (3.3%)	10 (6.1%)
Death without prior event	2 (2.2%)	3 (1.8%)

Abbreviations: BC= breast cancer; CNS= central nervous system; iDFS= invasive disease-free survival; n= number of participants reporting data; N= total participants in group; T-DM1= trastuzumab emtansine

Source: Table 2.10, p54 of the submission and percentages calculated during evaluation.

Note: *Patients who experience additional iDFS event(s) within 61 days of their 1st iDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Loco-regional recurrence; [3] Contralateral breast cancer; [4] Death without prior event.

Table 6: Site of first distant recurrence: KATHERINE, ITT

	T-DM1	Trastuzumab
	n/N (%) per event type N = 78	n/N (%) per event type N = 121
CNS	44 (56%)	31 (26%)
CNS only	37 (47%)	24 (20%)
CNS and at least one other distant recurrence	7 (9%)	7 (6%)
Lung/liver	22 (28%)	50 (41%)
Bone/bone marrow	8 (10%)	27 (22%)
Skin, subcutaneous tissue, and lymph nodes	3 (4%)	11 (9%)
Other	1 (1%)	2 (2%)

Abbreviations: CNS= central nervous system; n= number of participants reporting data; N= total participants in group; T-DM1= trastuzumab emtansine

Source: KATHERINE CSR p1093, percentages are the proportion of those with distant recurrence, calculated during evaluation.

Note: Values differ from those in Table 5, possibly because it only included iDFS events within a 61 day window of the first iDFS event. Patients who experience distant recurrence at more than one site at the time of first recurrence are counted in the category according to the following hierarchy: [1] CNS; [2] lung/liver; [3] bone/bone marrow; [4] Skin, subcutaneous tissue, and lymph nodes; [5] Other.

6.13 The results of the secondary outcomes from KATHERINE are summarised in Table 7.

Table 7: Results of the KATHERINE secondary efficacy outcomes (ITT)

Outcome	Number of patients with event (%)		Risk Difference (%) (95% CI) [^]	Hazard ratio (95% CI)	p-value (log-rank)
	T-DM1 (N=743) n (%)	Trastuzumab (N=743) n (%)			
iDFS-SPNBC	95 (12.8%)	167 (22.5%)	-9.7 (-5.8, -13.5)	0.51 (0.40, 0.66)	< 0.0001
DFS	98 (13.2%)	167 (22.5%)	-9.3 (-5.4, -13.2)	0.53 (0.41, 0.68)	< 0.0001
OS	42 (5.7%)	56 (7.5%)	-1.9 (0.6, -4.4)	0.70 (0.47, 1.05)	0.0848*
DRFI	78 (10.5%)	121 (16.3%)	-5.8 (-2.3, -9.2)	0.60 (0.45, 0.79)	0.0003

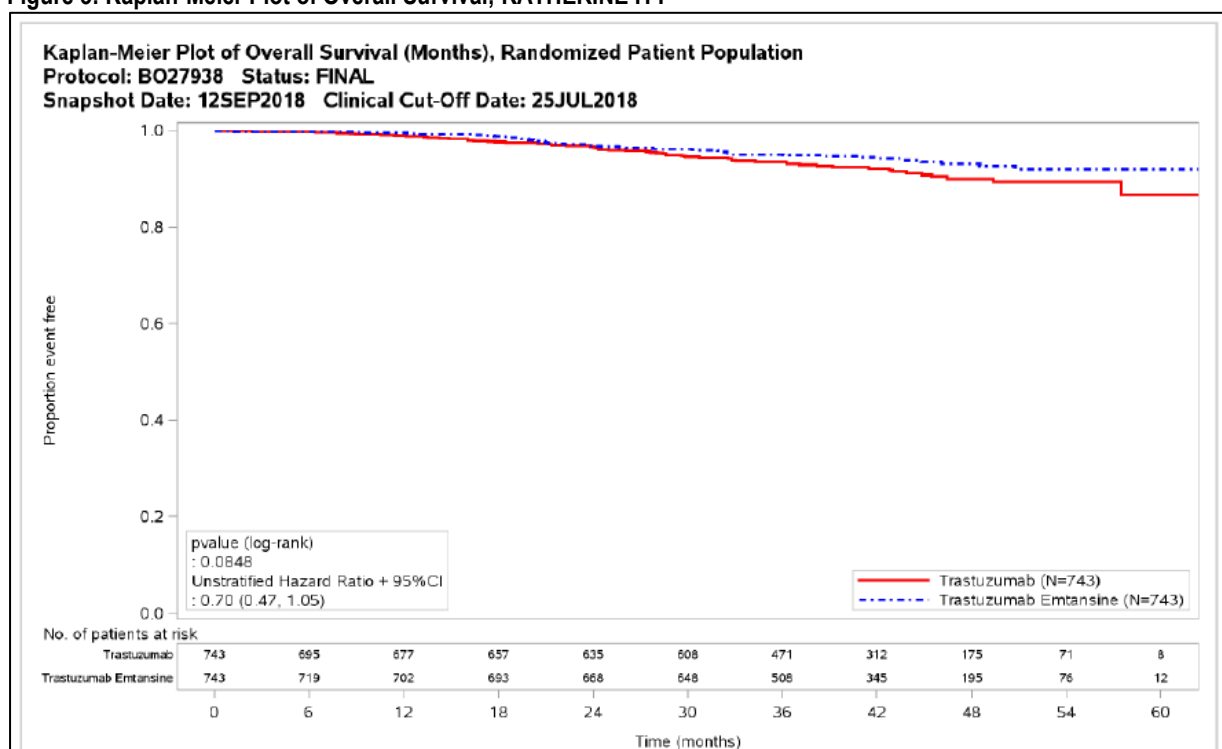
Abbreviations: CI= confidence interval; DFS= disease free survival; DRFI= distant relapse-free interval; iDFS= invasive disease-free survival; iDFS-SPNBC= invasive disease-free survival including second primary non-breast cancers; n= number of participants reporting data; N= total participants in group; OS= overall survival; T-DM1= trastuzumab emtansine

Source: Table ES.4, p.6 of the submission.

Notes: **Bold** indicates results of statistical significance. *The OS data were immature at the clinical cut-off date (98 events total); the final OS analyses is planned 119 months (367 events) from the enrolment of first patient to data cut-off. [^]Values calculated during the evaluation.

6.14 The submission reported that interim OS data were immature at the clinical cut-off date (25 July 2018, with 98 deaths reported; 42 in the T-DM1 arm and 56 in the trastuzumab arm). Final OS analyses are expected by March 2023 after 119 months (367 events) from first patient enrolment (April 2013). The submission claimed that the OS analysis did not cross the early stopping boundary, but that the OS result was supportive of the iDFS analysis (unstratified HR = 0.70, 95% CI: 0.47, 1.05, p=0.0848; see Figure 3). Given the immaturity of the OS data, there was no statistically significant difference in OS between the treatment groups.

Figure 3: Kaplan-Meier Plot of Overall Survival; KATHERINE ITT



Abbreviations: CI= confidence intervals; iDFS= invasive disease-free survival; ITT= intent-to-treat patients; N= total number of patients in arm; p= p value.

Source: Figure 2.4, p56 of the submission.

- 6.15 The submission provided results of pre-specified subgroup analyses for efficacy outcomes conducted within KATHERINE. The TGA CER noted that the clinical benefit of iDFS was demonstrable across the key subgroups, including those with hormone receptor-positive/negative HER2+ eBC, smaller volumes of residual invasive disease or Asian ethnicity (T-DM1 TGA CER, Section 8.1, p153). However, the subgroup analyses showed that the benefit was not statistically significant for patients aged ≥ 65 years or those treated with dual-targeted neoadjuvant therapy (i.e. pertuzumab); noting the similarity of the point estimates of effect and that the study may not have been powered to demonstrate these subgroup differences. The ESC noted the low number of patients in the subgroup of patients over 65 years and considered that the subgroup analyses did not identify any areas of concern to suggest there are likely to be differences in effectiveness in Australian patients.
- 6.16 The submission reported health-related quality of life (HRQoL) scores from EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires included in KATHERINE. Results from those questionnaires were similar between the two arms. However, when examined over the entire course of treatment, a higher proportion of patients in the T-DM1 arm experienced a clinically meaningful deterioration in role functioning, appetite loss, constipation, fatigue, nausea/vomiting, pain and systemic therapy side effects. In contrast, a lower proportion of patients in the T-DM1 arm had clinically meaningful

deterioration in diarrhoea compared to the trastuzumab arm as reported in the QLQ-C30 questionnaire.

Comparative harms

- 6.17 A summary of key adverse events (AEs) from KATHERINE is presented in Table 8. There were 212 (28.5%) and 135 (18.2%) patients who discontinued planned study treatment from the T-DM1 and trastuzumab arms respectively. The primary reasons for treatment discontinuation were AEs (18.0% and 2.1%), withdrawal of consent (6.6% and 7.7%) and progressive disease (2.2% and 5.2%) in the T-DM1 and trastuzumab treatment arms respectively. A total of 71 patients (8.7%) switched from T-DM1 to trastuzumab.
- 6.18 The incidence of AEs (any grade) and Grade ≥ 3 AEs was higher with T-DM1 versus trastuzumab; 98.8% vs. 93.3% for any grade and 25.7% vs. 15.4% for Grade ≥ 3 in the safety evaluable population. Grade ≥ 3 AEs occurring in at least 1.6% of patients in either arm were: platelet count decreased (5.7% vs. 0.3%), hypertension (2.0% vs. 1.3%) and hepatotoxicity (1.6% vs. 0.4%) for T-DM1 and trastuzumab respectively. As noted in the TGA CER (T-DM1 TGA CER, Section 8.2, p.154), adjuvant treatment with T-DM1 had an increased risk of toxicity compared with adjuvant trastuzumab due to the known toxicities of the maytansine conjugate of DM1 and a higher risk of long-term hepatic damage which was slow to resolve.
- 6.19 The most commonly reported AEs leading to discontinuation in the T-DM1 arm were: platelet count decreased (4.2%), blood bilirubin increased (2.6%), ejection fraction decreased (1.2%), aspartate aminotransferase (AST) increased (1.6%), alanine aminotransferase (ALT) increased (1.5%) and peripheral sensory neuropathy (1.5%). The PBAC noted that the TGA delegate's overview stated "treatment with trastuzumab emtansine requires more intensive monitoring than trastuzumab, particularly for haematological and hepatic abnormalities. Additional changes to the PI are warranted to support clinicians in managing the risks associated with this treatment".
- 6.20 There was one fatal AE which was deemed related to the study drug by the investigator: intracranial haemorrhage in a patient receiving T-DM1.

Table 8: Summary of key adverse events in KATHERINE, safety-evaluable set[^]

Adverse event (AE)	T-DM1 n (%) (N=740)	Trastuzumab n (%) (N=720)	RD (%) (95% CI)
Any AE	731 (98.8)	672 (93.3)	5.4 (3.5,7.4)
Grade ≥ 3 AEs	190 (25.7)	111 (15.4)	10.3 (6.2,14.4)
Serious AEs	94 (12.7)	58 (8.1)	4.7 (1.5, 7.8)
AEs leading to discontinuation of trial drug*	133 (18.0)	15 (2.1)	15.9 (12.9, 18.9)
AEs leading to dose modification/ interruption	196 (26.5)	37 (5.1)	21.4 (17.8, 24.9)
Treatment-related AEs* (any)	641 (86.6)	326 (45.3)	41.3 (36.9, 45.7)
Treatment-related serious AEs	39 (5.3)	8 (1.1)	4.2 (2.4, 5.9)
AEs leading to death	1 (0.1)	0 (0)	0.14 (-0.24, 0.51)
Total deaths	42 (5.7)	56 (7.8)	-2.1 (-5.0, 5.0)
Treatment-related deaths	1 (0.1)	0 (0)	0.14 (-0.24, 0.51)

Abbreviations: AE= adverse event; n= number of participants reporting data; N= total participants in group; RD= risk difference (numbers below zero favour T-DM1); RR= risk ratio (numbers below 1 favour T-DM1).

Source: Table 2.12, p58 of the submission and Table 2 von Minchkwitz et al 2019.

Notes:*only AEs related to T-DM1 were evaluated in the T-DM1 arm; ^ safety-evaluable population included all randomised patients who received any amount of study treatment (720 patients in the trastuzumab arm and 740 patients in the T-DM1 arm; **Bold** represents statistically significant difference between arms; the number of patients who switched from T-DM1 to trastuzumab due to AEs was not reported.

Benefits/harms

6.21 A summary of the comparative benefits and harms for T-DM1 versus trastuzumab is presented in Table 9.

Table 9: Summary of comparative benefits and harms for T-DM1 versus trastuzumab

Benefits						
iDFS (median duration of follow up 41 months)						
Event	T-DM1	Trastuzumab	Absolute Difference	HR** (95% CI)		
iDFS (median duration of follow up 41 months)						
iDFS, ITT population n/N (%)	91/743 (12.2%)	165/743 (22.2%)		0.50 (0.39, 0.64) P<0.0001)		
3-year event-free iDFS rate*, ITT population n/N (%)	88.27 (85.81, 90.72)	77.02 (73.78, 80.26)	11.25%			
OS (median duration of follow up 41 months)						
Deaths, ITT population n/N (%)	42/743 (5.7%)	56/743 (7.5%)		0.70 (0.47, 1.05) P=0.0848¹		
5-year event-free death rate*, ITT population n/N (%)	92.09 (89.44, 94.74)	86.79 (80.95, 92.63)	5.3%			
DRFI (median duration of follow up 41 months)						
DRFI, ITT population n/N (%)	78/743 (10.5%)	121/743 (16.3%)		0.60 (0.45, 0.79) P=0.0003		
Harms (safety-evaluable set)⁵						
	T-DM1 n/N (%)	Trastuzumab n/N (%)	RR (95% CI)	Event rate/100 patients		RD % (95% CI)
				T-DM1	Trastuzumab	
Any AE	731/740 (98.8%)	672/720 (93.3%)	1.06 (1.04, 1.08)	98.8	93.3	5.4 (3.5,7.4)
Grade ≥ 3 AE	190/740 (25.7%)	111/720 (15.4%)	1.67 (1.35, 2.06)	25.7	15.4	10.3 (6.2,14.4)
SAE	94/740 (12.7%)	58/720 (8.1%)	1.58 (1.16, 2.15)	12.7	8.1	4.7 (1.5, 7.8)
AEs leading to discontinuation ^a	133/740 (18.0%)	15/720 (2.1%)	8.63 (5.11, 14.57)	18.0	2.1	15.9 (12.9, 18.9)
Treatment-related serious AEs ^a	641/740 (86.6%)	326/720 (45.3%)	1.91 (1.76, 2.08)	86.6	45.3	4.2 (2.4, 5.9)
Grade ≥ 3 platelet count decreased	42/740 (5.7%)	2/720 (0.3%)	20.43 (4.96, 84.09)	5.7	0.3	5.4 (3.7, 7.1)
Grade ≥ 3 peripheral sensory neuropathy	10/740 (1.4%)	0/720 (0%)	20.43 (1.20, 348.05)	1.4	0	1.4 (0.5, 2.2)
Grade ≥ 3 Hyperkalaemia	9/740 (1.2%)	1/720 (0.1%)	8.76 (1.11, 68.94)	1.2	0.1	1.1 (0.2, 1.9)
Grade ≥ 3 Fatigue	8/740 (1.1%)	1/720 (0.1%)	7.78 (0.98, 62.08)	1.1	0.1	0.9 (0.1, 1.7)
Grade ≥ 3 Anaemia	8/740 (1.1%)	1/720 (0.1%)	7.78 (0.98, 62.08)	1.1	0.1	0.9 (0.1, 1.7)
Grade ≥ 3 Hepatotoxicity	12/740 (1.6%)	3/720 (0.4%)	3.89 (1.10, 13.73)	1.6	0.4	1.2 (0.2, 2.2)
SAE device related infections	6/740 (0.8%)	0/720 (0%)	12.65 (0.71, 224.12)	0.8	0	0.8 (0.1, 1.5)

Abbreviations: CI= confidence interval; DF= disease free; DFS= disease free survival; DRFI= distant relapse-free interval; iDFS= invasive disease-free survival; iDFS-SPNBC= invasive disease-free survival including second primary non-breast cancers; n= number of participants reporting data; N= total participants in group; OS= overall survival; SAE= serious adverse event; T-DM1= trastuzumab emtansine
Source: Table ES.4, p.6 and Table 2.9, p53, Table 2.11, p55, Table 2.12, p58, Table 2.17, p61 of the submission, Table 2 von Minchkwitz et al 2019 and calculated during evaluation.

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Notes: **Bold** indicates results of statistical significance. * 3-year and 5-year rates derived from Kaplan-Meier estimates; ** Estimated by Cox-regression. Due to stratum with <5 patients, table presents unstratified analyses for all endpoints. The OS data was immature at the clinical cut-off date (98 events total); the final OS analyses is planned 119 months (367 events) from the enrolment of first patient to data cut-off. ^ Only AEs related to T-DM1 were evaluated in the T-DM1 arm. §Safety-evaluable population included all randomised patients who received any amount of study treatment (720 patients in the trastuzumab arm and 740 patients in the T-DM1 arm. The number of patients who switched from T-DM1 to trastuzumab due to AEs was not reported. Absolute difference, relative risk and risk difference values were calculated during evaluation using RevMan version 5.3.

6.22 On the basis of direct evidence presented in the pivotal KATHERINE trial, for every 100 patients treated with T-DM1 in comparison to trastuzumab after three years (based on KM estimates):

- Approximately 11 additional patients would not experience recurrence (return of invasive disease).
- Approximately 11 additional patients would not experience locoregional recurrence (return of invasive disease including a second primary non-breast cancers).
- Approximately 11 additional patients would not experience distant recurrence.

On the basis of direct evidence presented in the pivotal KATHERINE trial, for every 100 patients treated with T-DM1 in comparison to trastuzumab over a median duration of follow-up of 41 months:

- Approximately 10 additional patients would experience a grade ≥ 3 AE, including 5 experiencing decreased platelet counts, 1 experiencing peripheral sensory neuropathy (a sensation of tingling/burning in the hands or feet), 1 experiencing hyperkalaemia, 1 experiencing fatigue, 1 experiencing anaemia and 1 experiencing hepatotoxicity.
- Approximately 5 additional patients would experience an SAE, including 1 experiencing a device related infection (an infection at the site where the catheter is inserted for drug dosing).

Clinical claim

6.23 The submission described T-DM1 as superior in terms of effectiveness and inferior in terms of safety compared to trastuzumab. The commentary considered that the clinical claim was supported by the evidence with respect to iDFS, but not OS. Previously, the ESC noted that a statistically significant difference in iDFS is difficult to interpret in the absence of a difference in OS (Neratinib PSD, March 2019, paragraph 6.37); however the ESC noted that this was in the context of a poorer quality trial and a considerably smaller absolute benefit in iDFS. The TGA Delegate's Overview noted that longer term data were required to determine whether the observed improvement in iDFS translates into an OS benefit (T-DM1 TGA Delegate's Overview, p12). While OS data were immature, the ESC considered that, on balance, the data support a difference in favour of T-DM1. The ESC agreed with the commentary that the clinical claim was supported with respect to iDFS and considered that a gain in OS is plausible but is of uncertain magnitude due to the immaturity of the data.

- 6.24 The safety profile of T-DM1 in KATHERINE was consistent with prior experience with T-DM1 in mBC. The submission acknowledged the inferiority of T-DM1 relative to trastuzumab in terms of the higher incidence of Grade 3 or 4 TEAEs, TEAEs leading to discontinuation and TEAEs leading to dose reduction as would be expected, given its targeted cytotoxic component (DM1). The submission stated that adverse events were manageable with minimal impact on HRQoL. It was appropriate to claim inferior safety, however, the ESC considered the claim of minimal impact on HRQoL was not demonstrated in the submission. Such a claim would have required an assessment of HRQoL according to the occurrence of AEs; this was not provided by the submission. The ESC noted that over the course of treatment, patients in the T-DM1 group had clinically meaningful deterioration in some domains of HRQoL questionnaires (see paragraph 6.16). The PSCR noted that there were no differences between treatment arms in the overall HRQoL scores over the course of treatment.
- 6.25 The PBAC considered that the claim of superior comparative effectiveness in terms of iDFS was reasonable and adequately supported by the data. The PBAC also considered that a gain in OS is plausible based on the KATHERINE trial but is of uncertain magnitude due to the immaturity of the data.
- 6.26 The PBAC considered that the claim of inferior comparative safety was reasonable. The PBAC noted that the safety profile for T-DM1 is well documented as it has been used in the metastatic breast cancer treatment and considered it to be manageable. The PBAC considered that the claim of minimal impact of HRQoL was not supported by the evidence, given the higher rates of adverse events in the T-DM1 arm. Further, the PBAC considered that the use of EQ-5D-3L to capture quality of life is unlikely to be sufficiently sensitive.

Economic analysis

- 6.27 The submission presented a stepped economic evaluation based on KATHERINE and implemented a modelled cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) for T-DM1 vs. trastuzumab. Health benefits were reported as life years gained (LYGs) and quality adjusted life years (QALYs) gained, respectively. The latest iDFS data were used for the economic analysis (cut-off 25th July 2018). The key components of the economic evaluation comparing T-DM1 with trastuzumab are summarised in Table 10.

Table 10: Summary of model structure and rationale

Component	Summary
Time horizon	40 years in the model base case versus 62.6 months in trial.
Outcomes	LYG, QALY
Methods used to generate results	Markov model, extrapolated from median point of follow-up from KATHERINE (41.2 months) using the exponential parametric function applied to the iDFS data.
Health states	Six health states: iDFS, locoregional recurrence, remission, distant recurrence (1st line mBC, 2nd line mBC), death.
Cycle length	1 week
Transition probabilities	iDFS, locoregional recurrence, remission and death in the eBC setting sourced from KATHERINE. Progression and OS in the mBC setting sourced from CLEOPATRA and EMILIA. Distant recurrence from remission was based on a study reported by Hamilton (2015). Death also from ABS Life Tables.
Utilities	Derived from KATHERINE and literature (mBC from Lloyd 2006).

Abbreviations: ABS= Australian Bureau of Statistics; eBC= early breast cancer; iDFS= invasive disease-free survival; LYG= life year gained; mBC= metastatic breast cancer; OS= overall survival; QALY=quality adjusted life year.

Source: Table 3.2, Table 3.9, p. 75-94 of the submission and Section 3.8.3, p. 104 of the submission.

- 6.28 The submission subdivided both mBC health states into early and late recurrence to more accurately model the disease course of mBC. This was appropriate.
- 6.29 The submission applied utilities for the mBC health states based on the utility algorithm published by Lloyd (2006). The submission justified its use of the algorithm on the basis that it was used for the 2014 trastuzumab/pertuzumab/T-DM1 mBC PBAC resubmission. However, the submission did not provide its assumptions for the inputs used for the utility algorithm and the resulting values were lower than those used in the 2014 resubmission, most likely due to a different patient population. Utility values were an important driver of the ICER. The ESC considered that the use of the EQ-5D-3L data from the trial to capture quality of life for the iDFS (on and off treatment), locoregional recurrence and remission health states may not be appropriate as this instrument is unlikely to be sufficiently sensitive. Further, the ESC noted that pooled utilities from both KATHERINE arms were applied to these health states. The use of pooled data was not reasonable as T-DM1 patients had a wider range of HRQoL losses while on treatment, though the impact is likely to be small as mean scores across the arms were similar. Given the higher rates of adverse events in the T-DM1 arm, using a more sensitive instrument would be likely to increase the ICER.
- 6.30 A summary of the key drivers of the model is shown in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact Base ICER: \$ [REDACTED]
Time horizon	Model adopted a 40-year time horizon. This is relatively long given the median age at diagnosis with HER2+ eBC for women in Australia is 58.5 years (IPSOS 2018).	Moderate, favours T-DM1 ICER: 20 years \$ [REDACTED].
Extrapolation – Time limited treatment effect and sustained remission adjustment	The submission extrapolated the treatment effect to 7 years, with linear convergence to an iDFS HR of 1 (null treatment effect) over a three-year period (until year 10) based on the HERA and BCIRG-006 study evidence. This evidence was also used to support the sustained remission adjustment (where risk of recurrence started to decrease at 42 months).	Moderate, favours T-DM1 ICER: Treatment effect starts decreasing at 41.2 months (median point of follow-up): \$ [REDACTED] High, favours T-DM1 ICER: No sustained remission adjustment \$ [REDACTED]
Utilities	The model adopted utilities from KATHERINE for eBC and Lloyd (2006) for mBC. The submission assumed the utility was the same for a patient in the iDFS and locoregional recurrence states. The mBC utilities used in the model are lower than those used in 2014 (from Lloyd, 2006), most likely due to a different patient population.	Moderate, favours T-DM1 ICER: \$ [REDACTED] (utilities from Hedden 2012) Low, favours trastuzumab ICER: \$ [REDACTED] (utilities from Rautalin 2017) ICER: \$ [REDACTED] (utilities from Lidgren 2007)

Abbreviations: HR= hazard ratio; ICER= incremental cost effectiveness ratio; T-DM1= trastuzumab emtansine
Source: Table 3.2, p75 and Section 3.4.3 p87-92 of the submission.

- 6.31 The ESC noted that the model was driven by OS (extrapolated from iDFS) however there was no statistically significant OS benefit demonstrated in the KATHERINE trial and, as the data are immature, the magnitude of OS benefit remains uncertain.
- 6.32 The submission directly applied iDFS from KATHERINE in order to determine incremental differences in OS, and hence used iDFS as a surrogate for OS since OS data from KATHERINE were immature. However, the submission and PSCR did not address the requirements for supporting the use of surrogate outcomes. The submission claimed that the PBAC previously recognised DFS as a surrogate endpoint for OS in the 2006 trastuzumab eBC submission (implied in trastuzumab PSD, July 2006, p6). While DFS may have previously been accepted as a surrogate for OS in the context of the use of exemestane for the treatment of eBC, the ESC noted that the surrogate framework requests that evidence be presented to support the application of previously established surrogate relationships in the context of the proposed medicine.
- 6.33 The submission subsequently used data from Hamilton 2015, EMILIA and CLEOPATRA to estimate the proportion of women experiencing distant disease and mortality from distant disease. Arguably, the commentary noted the key surrogacy relationship is defined by the link between distant recurrence and OS; the bulk of the modelled difference in recurrence events is due to distant disease. The ESC noted there were significant transitivity issues between patients in Hamilton 2015, EMILIA and CLEOPATRA and the proposed patient population. Patients in Hamilton 2015 did not receive any form of targeted therapy; patients in EMILIA were younger (53 vs 58.5

years) and a significantly smaller fraction received trastuzumab (16% vs. 100%) or endocrine therapy (41% vs. 81%) in the eBC setting; patients in CLEOPATRA were younger (54 vs. 58.5 years) and a significantly smaller fraction received prior trastuzumab (11% vs. 100%), endocrine therapy (25% vs. 81%) or taxane therapy (23% vs. 100%). The ESC considered that it was unclear how these transitivity issues affected the ICER.

- 6.34 The submission extrapolated the treatment effect to 7 years, with linear convergence to an iDFS HR of 1 (null treatment effect) over a three-year period (until year 10) based on the HERA and BCIRG-006 study evidence. The ESC questioned whether the annualised hazard rates from these studies supported the ongoing benefit up to 10 years, but noted that there was some evidence to support ongoing benefit beyond 5 years.
- 6.35 The submission applied a sustained remission adjustment from the point of median follow-up (42 months). After 42 months, the proportion of patients in the remission health state who achieve sustained remission was linearly increased to the set maximum (95%) at ten years based on the HERA and BCIRG-006 study 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. The commentary considered this to be questionable due to transitivity issues between patients in HERA and BCIRG-006 and the proposed patient population. Transitivity issues arose between these studies and KATHERINE predominantly due to patient age and prior therapies. The ESC agreed with the commentary that the transitivity of HERA and BCIRG-006 may be an issue but noted it was difficult to quantify the impact of these differences. The ESC considered that based on data from HERA and BCIRG-006 an adjustment may have been appropriate, however setting the maximum to 95% at ten years was optimistic. The PBAC agreed with the ESC that it was reasonable to assume some degree of sustained remission.
- 6.36 The PBAC considered that the time horizon applied (40 years) was inappropriate as the median age at diagnosis with HER2+ early breast cancer (eBC) for women in Australia is 58.5 years. Further, the model relied on an OS gain (extrapolated from iDFS) that was assumed to persist for 40 years despite the OS results from the KATHERINE trial being immature and not statistically significant. The PBAC considered that greater confidence in establishing cost-effectiveness would be derived by limiting the time horizon to 20 years, and noted this resulted in an ICER that was within an acceptable range (less than \$15,000 per QALY).
- 6.37 A stepped economic evaluation was presented in the submission (see Table 12). The submission presented Step 1 as a within trial analysis (62.6 months follow-up), Step 2 extrapolated to the time horizon of 40 years, Step 3 applied a time-limited treatment effect, Step 4 applied a sustained remission adjustment, Steps 5, 6 and 7 included

medical resource use costs, AE costs and end-of-life costs and Step 8 applied HRQoL to transform LYs into QALYs.

- 6.38 The commentary noted that the ICER increased to less than \$15,000/QALY when the weighted price for trastuzumab (including the prices for mBC and gastric cancer) was applied to the Markov model in the eBC setting (corrected to less than \$15,000/QALY when the weighted price was applied in both the eBC and mBC settings in the model, as identified in the pre-PBAC response). The PBAC considered that using the indication-specific prices for trastuzumab in eBC and mBC was an appropriate approach in this case, in order to reflect the prices considered cost-effective in the relevant settings. The PBAC noted that the base case ICER, proposed in the pre-PBAC response was less than \$15,000/QALY using the indication-specific prices and updated dispensing fees and corrected MBS costs for IV administration and specialist visits.
- 6.39 The ESC noted that the downstream costs represented significant cost offsets which were attributed to delayed or prevented recurrence. The ESC noted that the unit costs appear reasonable but that these cost offsets relied on extrapolation of the iDFS results, and assumptions regarding the tapering of effect and reduced recurrence hazard that introduced uncertainty in the modelled outcomes and costs.

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Table 12: Results of the stepped economic evaluation

Step and component	T-DM1	Trastuzumab	Increment
Step 1: trial-based costs and outcomes (5* year data)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	4.567	4.488	0.079
Incremental cost/extra LYG gained			\$ [REDACTED]
Step 2: time horizon extrapolated to 40 years			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	12.483	10.874	1.609
Incremental cost/extra LYG gained			\$ [REDACTED]
Step 3: Applying time limited treatment effect up to year 10			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	11.810	10.874	0.935
Incremental cost/extra LYG gained			\$ [REDACTED]
Step 4: Applying sustained remission adjustment			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	13.229	11.991	1.239
Incremental cost/extra LYG gained			\$ [REDACTED]
Step 5: Incorporation of MRU costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	13.229	11.991	1.239
Incremental cost/extra LYG gained			\$ [REDACTED]
Step 6: Incorporation of AE related costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	13.229	11.991	1.239
Incremental cost/extra LYG gained			\$ [REDACTED]
Step 7: Inclusion of end of life costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	13.229	11.991	1.239
Incremental cost/extra LYG gained			\$ [REDACTED]
Step 8: Incorporation of utility values to determine QALYs (base-case analysis)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained (base case)			\$ [REDACTED]

Source: page 5, pre-PBAC response

Updates applied in economic evaluation.xlsx:

Updated trastuzumab ex-manufacturer price: eBC: 150mg: \$ [REDACTED], 60mg: \$ [REDACTED]; mBC: 150mg: \$ [REDACTED], 60mg: \$ [REDACTED]

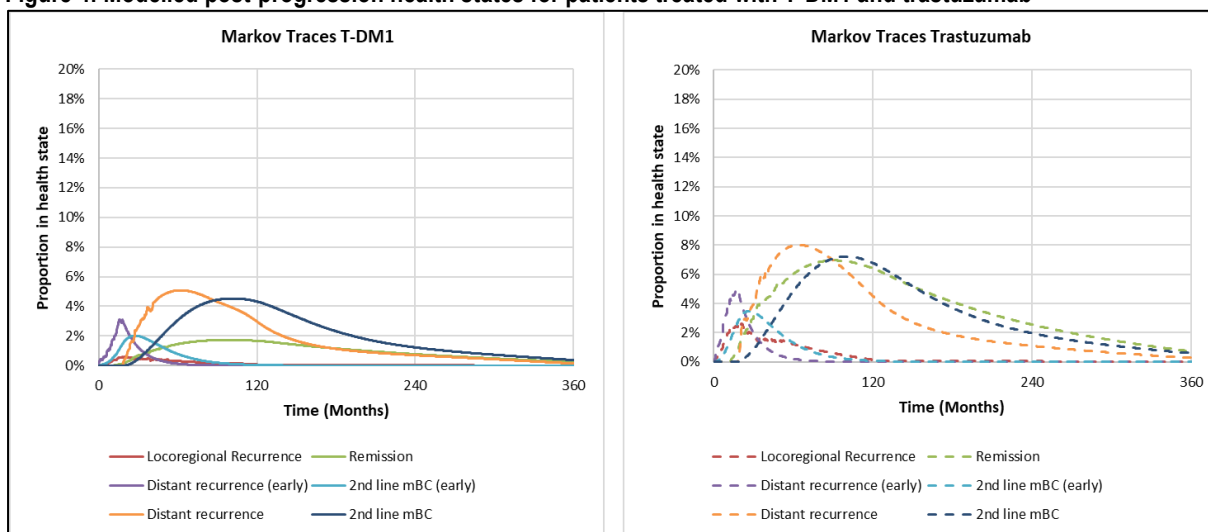
Replaced MBS item 13918 with MBS item 13915 (\$66.10)

Updated MBS item 105 to current fee: \$44.35

Updated PBS fees to current amounts: Public: \$85.06, Private: \$124.82, Private for trastuzumab: \$97.80

6.40 Traces for the model results are presented in Figure 4. Time spent in the iDFS health state is the key driver of the clinical benefit in the model.

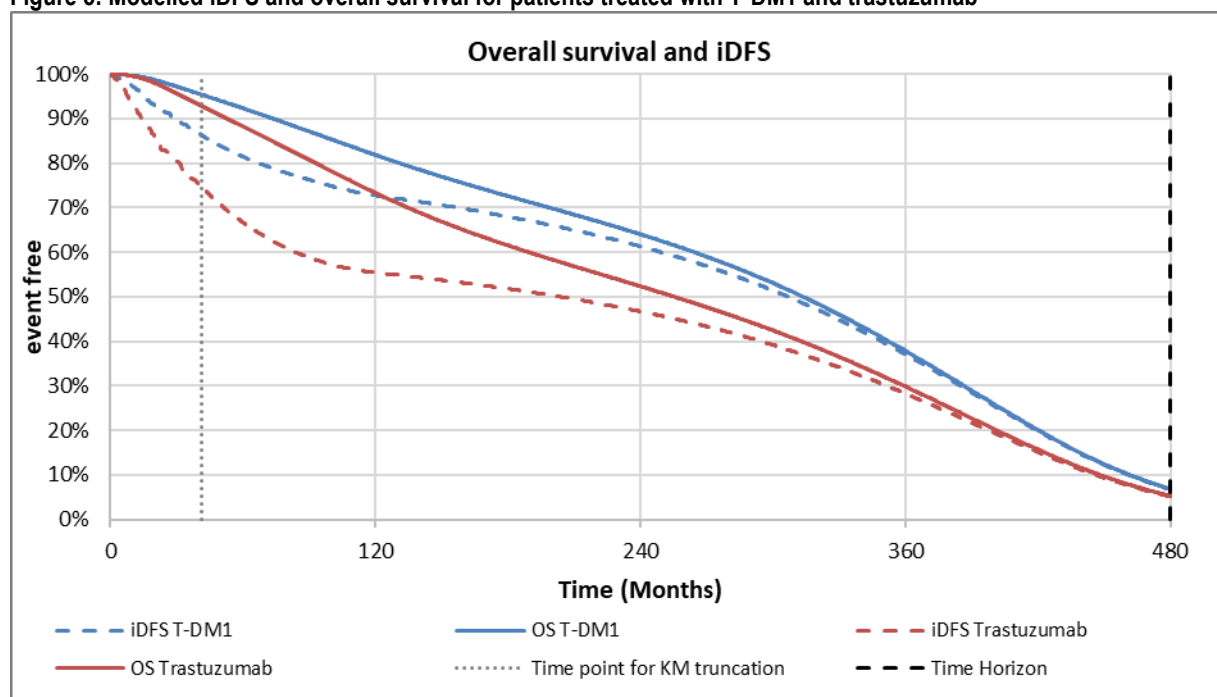
Figure 4: Modelled post-progression health states for patients treated with T-DM1 and trastuzumab



Abbreviations: mBC= metastatic breast cancer; T-DM1= trastuzumab emtansine
Source: Figure 3.12, p103 of the submission.

6.41 The submission presented Markov traces showing the proportion of patients in the iDFS health state and alive at any given time over the 40-year time horizon (Figure 5).

Figure 5: Modelled iDFS and overall survival for patients treated with T-DM1 and trastuzumab



Abbreviations: iDFS= invasive disease-free survival; KM= Kaplan Meier; OS= overall survival; T-DM1= trastuzumab emtansine.
Source: Figure 3.11, p102 of the submission.

6.42 The number of recurrence events and resulting number of recurrences avoided by substituting trastuzumab with T-DM1 for the trial duration and the time horizon of the

economic evaluation are presented in Table 13. These results indicate that while the model predicts a doubling in the recurrence events avoided over time (40 years), the allocation of those events is weighted towards distant disease; the base case ICER largely relies on avoiding distant recurrence in 16% of patients over a 40-year time horizon. Over the 40-year time horizon the model estimated that each patient treated with T-DM1 gained 2.973 life years (297.3 per 100 patients, undiscounted). Thus, there were 12.1 (297.3/24.5) life years gained per recurrence avoided or 18.7 (297.3/15.9) life years gained per distant recurrence avoided. Since the occurrence of distant events relies on applying transitional probabilities from studies outside of KATHERINE to the KATHERINE trial, this increases the uncertainty associated with those estimates.

Table 13: Recurrence events (undiscounted)

Recurrence event	T-DM1	Trastuzumab	Incremental outcome (per 100 patients)
LYG	23.797	20.824	2.973 (297.3 per 100 patients)
Total trial duration (62.6 months trial duration; Step 1)			
Locoregional recurrence	2.0%	7.3%	-5.3
Distant recurrence	14.2%	20.9%	-6.7
Any recurrence	16.1%	28.1%	-12.0
Model time horizon (40 years; Step 8)			
Locoregional recurrence	3.3%	11.8%	-8.6
Distant recurrence	25.7%	41.7%	-15.9
Any recurrence	29.0%	53.5%	-24.5

Abbreviations: LTG= life year gained; T-DM1= trastuzumab emtansine
Source: Table 3.15, p103 of the submission.

- 6.43 Results of univariate and multivariate sensitivity analyses specified by the submission and additional analyses conducted during the evaluation are presented in Table 14. For the univariate analyses conducted during the evaluation, the ICER was most sensitive to reducing the time-horizon to 20 years (increased to less than \$15,000/QALY) and removing the sustained remission adjustment (increased the ICER to \$15,000/QALY - \$45,000/QALY).
- 6.44 The multivariate analysis with a 20-year time horizon, no sustained remission adjustment and corrected transition probabilities had the largest impact on the ICER (increased to \$15,000 - \$45,000 per QALY gained). The PBAC noted that for this relatively conservative multivariate analysis the ICER remained under \$45,000 per QALY. The ESC noted that although some uncertainties remained, particularly around ongoing treatment effects and the sustained remission adjustment; the ESC considered the sensitivity analyses indicated that the model results were reasonable and fairly robust within plausible ranges of parameters.

Table 14: Results of univariate and multivariate sensitivity analyses

Variable or assumption	Base case value	T-DM1 versus trastuzumab		
		Incr cost	Incr effectiveness (QALYG)	ICER (per QALYG)
Base case		\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
20-year time horizon	40-year time horizon	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Utilities from Rautalin (2017)	Utilities from KATHERINE for eBC and Lloyd (2006) for mBC	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Utilities from Hedden (2012)		\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Utilities from Lidgren (2007)		\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
TP = 0.0019 Remission to 1st line mBC (based on median survival 7.0 years from Hamilton 2015)	0.0017 (median survival of 7.6 years)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Treatment effect starts decreasing at 62.6 months (end of trial period)	Treatment effect starts decreasing at 84 months to the null effect at 120 months.	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Treatment effect starts decreasing at 41.2 months (median point of follow-up)		\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Sustained remission adjustment (max proportion achieving sustained remission 75%)	Sustained remission adjustment (max proportion achieving sustained remission 95%)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Sustained remission adjustment (risk of recurrence starts to decrease at 30 months)	Sustained remission adjustment (risk of recurrence starts to decrease at 42 months)	\$ [REDACTED]	[REDACTED] [*]	\$ [REDACTED]
Sustained remission adjustment – remove	Sustained remission adjustment	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Multivariate: 20-year time horizon, TP = 0.0019, sustained remission adjustment 75%, risk of recurrence starts to decrease at 30 months		\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Multivariate: 20-year time horizon, TP = 0.0019, no sustained remission adjustment		\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Abbreviations: eBC= early breast cancer; iDFS= invasive disease-free survival; ICER= incremental cost effectiveness ratio; Incr= incremental; ISH= in situ hybridization; IV= intravenous; mBC= metastatic breast cancer; MBS= Medicare Benefits Schedule; QALYG= quality adjusted life year gained; TP= transition probability.

Source: Table 16, page 6 of pre-PBAC response.

The redacted table shows ICERS in the range of less than \$15,000/QALY - \$45,000/QALY.

Drug cost/patient/course

6.45 The submission reported a drug acquisition cost for a complete treatment course of 14 three-weekly cycles of T-DM1 of \$ [REDACTED] per patient (updated cost for a complete treatment course of 14 cycles taking into account PBS fees as of July 2019 and using the weighted DPMA per administration across the public and private settings;

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\$ [REDACTED] × 14). The average treatment duration in KATHERINE was 11.9 cycles, resulting in an average cost per patient of \$ [REDACTED]. The PBAC noted this cost is significantly higher than the drug acquisition cost for a complete treatment course of 17 three-weekly cycles of trastuzumab of \$ [REDACTED] per average patient (see Table 15).

Table 15: Drug cost per patient for proposed drug compared within trial (KATHERINE), Markov model and financial estimates

	T-DM1		Trastuzumab	
	Within trial (62.6 months) Model (40-yr time horizon)	Financial estimates	Within trial (62.6 months) Model (40-yr time horizon)	Financial estimates
Mean dose (mg/infusion)	250.4	250.4	1 st cycle: 484.1 2 ^{nd+} cycle: 432.3 All cycles: 438.0	447
Mean duration (3-weekly cycles) ^b	11.9	11.9	12.7	12.0
Total mean administered (mg)	2,970 (trial) 2,980 ^c (trial and model analysis)	2,980 ^c	5,546 (trial) 5,563 ^d (trial and model analysis)	5,364 ^{a,c}
Drug cost/patient/cycle	\$ [REDACTED]	\$ [REDACTED]	1 st : \$ [REDACTED] 2 ^{nd+} : \$ [REDACTED]	\$ [REDACTED]
Drug cost/patient/course	\$ [REDACTED] ^d	\$ [REDACTED] ^f	\$ [REDACTED]	\$ [REDACTED] ^f

Abbreviations: mg= milligram; T-DM1= trastuzumab emtansine

Source: Section 3.6.1.2-3.6.1.3, p96-98, Section 4.2.1, p124 of the submission, saf_cumdose_CSRINT_SE.xls workbook, 'Results' tab of the Economic Evaluation.xls workbook, 3a and 3b tabs of the utilisation-and-cost-model. Italicised values were calculated during evaluation. a average treatment costs were only estimated based on cost of trastuzumab IV (did not consider the subcutaneous (SC) form since it was cost-minimised to IV trastuzumab in 2015.

b mean number of 3-weekly cycles for planned study treatment (excludes patients who switched to trastuzumab).

c calculated from mean dose x number of cycles for comparison with trial cumulative actual dose

d calculated from mean dose x number of cycles for comparison with trial cumulative actual dose

e calculated by multiplying cost per cycle x number of cycles

Estimated PBS usage & financial implications

6.46 This submission was considered by DUSC. The submission used a modified market share approach incorporating additional market and clinical inputs to quantify the market for the proposed population. This was reasonable given that utilisation details for a full market share approach cannot be obtained from current PBS descriptors for adjuvant eBC treatment following neoadjuvant therapy. The submission used the most recent 12 months of data available from Medicare Australia PBS Statistics to quantify the current market size and structure.

6.47 The submission did not provide an estimate of the number of grandfathered patients to be included and made no provision for grandfathered patients in the financial estimates. The PSCR stated that the number of grandfathered patients was not estimated in the submission since these numbers were implicitly included in the estimates derived from the market share approach. The DUSC agreed this was appropriate.

6.48 The financial implications of listing adjuvant T-DM1, as estimated in the submission, are presented in Table 16. The submission estimated that the total financial implications to the PBS/RPBS/MBS over the first 6 years would be \$60 - \$100 million.

Table 16: Estimated use and financial implications (as presented in submission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed*	█	█	█	█	█	█
Estimated financial implications of T-DM1						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments**	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Estimated financial implications for trastuzumab						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net financial implications no copayments						
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to PBS/RPBS/MBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Abbreviations: MBS= Medicare Benefits Schedule; PBS= Pharmaceutical Benefits Scheme; RPBS= Repatriation Pharmaceutical Benefits Scheme.

Source: Table 4.8, p138 and Table 4.12, p129 of the submission and calculated during evaluation from '4b. Displaced - PUB', worksheets within the Utilisation and cost model.xlsx

Notes: * Assuming a script equivalence of 1.0 between T-DM1 and trastuzumab. ** based on trastuzumab use currently.

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

6.49 DUSC considered the estimates presented in the submission to be overestimated in years 1 and 2, and underestimated in years 3 to 6. DUSC developed revised estimates applying the following assumptions:

- The proportion of patients receiving neoadjuvant treatment was changed from 46% in year 1 and up to 52% in year 6; to 27% in year 1 and up to 75% in year 6. DUSC considered that the assumption that 46% of patients receive neoadjuvant therapy in year 1 was inconsistent with the analysis of the full PBS data. DUSC commented that neoadjuvant therapy is becoming more common, and considered that over the next five years there may be a significant shift in the treatment algorithm to neoadjuvant therapy becoming standard of care for the majority of patients. DUSC estimated that the proportion of neoadjuvant therapy could increase to 75% by year 6. The Pre-PBAC response argued that this was overestimated and unsubstantiated, and maintained that 52% is the maximum proportion of patients who will receive neoadjuvant therapy as only patients with high risk eBC (lymph node positive and/or tumour >2cm) are likely to be suitable for neoadjuvant therapy. The PBAC agreed with the pre-PBAC response and considered that the neoadjuvant treatment rate should be 27% in Year 1 increasing

to 52% in year 3.

- The proportion of patients self-funding neoadjuvant pertuzumab was revised from 40% to 20%. The submission's estimate of 40% was based on current enrolment in HER START (Roche medicines access program). This is significantly higher than the 18% of patients who received pertuzumab in KATHERINE. DUSC considered there would be fewer patients willing to pay for pertuzumab once T-DM1 is PBS listed, and that the upper estimate of the proportion of patients using pertuzumab would be 20%. The pre-PBAC response stated that the sponsor is seeking PBS listing of neoadjuvant pertuzumab at the March 2020 PBAC meeting, which, if recommended, would increase use of pertuzumab compared with the current self-funded arrangement. The pre-PBAC response presented two sets of utilisation estimates: one assuming neoadjuvant pertuzumab is PBS-listed; and one reflecting the current funding scenario where neoadjuvant pertuzumab is not PBS-listed, which assumed 20% of patients use neoadjuvant pertuzumab in line with the DUSC advice. The PBAC considered that it would be appropriate to assume no PBS subsidy of pertuzumab in the financial estimates (given this reflects the current funding situation).
- For patients not treated with neoadjuvant pertuzumab, the proportion of patients with residual disease was changed from 78.5% to 50%. The commentary noted that residual disease rates (1 – pCR rates) were based on a phase II RCT (NEOSPHERE, Gianni 2012) that assessed chemotherapy plus trastuzumab (78.5%) and chemotherapy plus trastuzumab and pertuzumab (60.7%). There were significant transitivity issues between NEOSPHERE patients and the proposed patient population. Patients in NEOSPHERE had either early, inflammatory or locally advanced HER2+ BC which means only 29% were node negative, compared to 46 – 69% of the proposed population. DUSC considered that the NEOSPHERE trial was not suitable for benchmarking pCR rates as patients in this trial were not treated with neoadjuvant anthracyclines. DUSC noted that the pCR in patients treated with chemotherapy plus trastuzumab in NEOSPHERE was well below the pCR from multiple studies that included treatment with anthracycline plus taxane plus trastuzumab^{3,4,5} and therefore considered the estimated residual disease rate of 78.5% is likely overestimated, and is likely to be closer to 50%. The pre-PBAC response and PBAC accepted this amendment as proposed by DUSC.

³ Buzdar AU et al. Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2013;14(13):1317. Epub 2013 Nov 13.

⁴ Robidoux A, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2013 Nov;14(12):1183-92. Epub 2013 Oct 4.

⁵ Untch M et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol.* 2012 Feb;13(2):135-44. Epub 2012 Jan 17.

- For patients treated with neoadjuvant pertuzumab, DUSC considered that the proportion of patients with residual disease should be kept at 60.7%, as estimated in the submission. However, the pre-PBAC response stated that a residual disease rate of 33% should have been used based on the PERSIA and TRYPHAENA trials.^{6,7} The PBAC considered the rate used in the pre-PBAC response (residual disease rate of 33% for patients treated with neoadjuvant pertuzumab) may be a reasonable estimate. However, the PBAC also noted that there is uncertainty in the pCR rate with neoadjuvant pertuzumab since there are different neoadjuvant chemotherapy regimens being used in different trials. The PBAC noted that evaluation of this rate was not conducted as part of this submission.
- The uptake was changed from 70% in all years in the submission; to 70% in year 1 increasing to 95% in year 4. DUSC considered that among patients who have proceeded with neoadjuvant treatment, the uptake of T-DM1 is likely to be higher than 70%. The pre-PBAC response and PBAC agreed with DUSC that uptake is likely to be 70% in year 1 increasing to 95% in year 4.

6.50 DUSC considered that MBS costs should be included for T-DM1 as local protocols (EviQ) and the KATHERINE trial mandated three weekly blood tests (FBC, EUC, LFT), while trastuzumab does not require blood test monitoring. The pre-PBAC response and PBAC accepted that these MBS costs should be included. DUSC commented that the other assumptions in the submission, such as the dosage, number of cycles per patient and the annual growth rate were reasonable.

6.51 Table 17 summarised the changed assumptions proposed by the pre-PBAC response and agreed by the PBAC.

Table 17: Summary of assumption changes

Assumption	Neoadjuvant treatment rate	Neoadjuvant P+H treatment rate	Residual disease rate (1-pCR) H+Chemo	Residual disease rate (1-pCR) P+H+Chemo	Treatment uptake rate
Submission	46% to 52%	40%	79%	61%	70%
DUSC proposal	27% to 75%	20%	50%	61%	70% to 95%
Pre-PBAC and PBAC	27% to 52%	20% ^a	50%	33%	70% to 95%

Source: Table 1, p2 of Pre-PBAC response

^a Scenario where pertuzumab is not PBS-subsidised, per footnote to Table 2 of the pre-PBAC response

6.52 Table 18 summarises the estimated use and financial implications proposed by the pre-PBAC response and agreed by PBAC (however, the PBAC considered that further

⁶ Lok. Pertuzumab Study for HER2-Positive Non-Metastatic Breast Cancer in the Neoadjuvant Setting in Australia: Interim Analysis. San Antonio Breast Cancer Symposium. 2019.

⁷ Schneeweiss A, Chia S, Hickish T, 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). *Ann Oncol.* 2013;24(9):2278-84

cost-offsets are required, as discussed below).

Table 18: Estimated use and financial implications proposed by pre-PBAC response and agreed by PBAC

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated financial implications of T-DM1						
Cost to PBS/RPBS less copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated financial implications for trastuzumab (comparator substitution costs only, does not account for cost-offsets for reduced use of trastuzumab in mBC)						
Cost to PBS/RPBS less copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net financial implications no copayments						
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS/PBS/RPBS ^b	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 2, p2 of Pre-PBAC response and revised Utilisation and cost model

^a Scenario where pertuzumab is not PBS-subsidised, per footnote to Table 2 of the pre-PBAC response ('Market model' worksheet Row 18 was changed to 20%)

^b '8. Net cost to Govt' worksheet Row 17 was amended to reference '6. Net changes - MBS!C77

The redacted table shows that at Year 6 the estimated net cost to the PBS/RPBS was \$10 - \$20 million.

6.53 The PBAC noted that cost offsets (for pertuzumab, trastuzumab and T-DM1) were included in the economic model for subsequent treatments due to a reduction in metastatic disease, including within the first 6 years. However, these cost offsets were not included in the financial estimates. The PBAC noted that most recurrences occur within 5 years after adjuvant therapy, the vast majority being distant recurrences, as shown in the HERA and KATHERINE trials. For patients treated with trastuzumab and pertuzumab in the first line mBC setting the median PFS from CLEOPATRA was 18.7 months. As such, the PBAC considered that most patients with recurrence would progress to second-line treatment with T-DM1 within 6 years after adjuvant therapy. The PBAC considered that cost offsets for pertuzumab, trastuzumab and T-DM1 should be included in the financial estimates consistent with the cost offsets estimated in the economic model.

Quality Use of Medicines

6.54 The submission did not present a discussion of the quality use of medicines associated with the listing of T-DM1.

Financial Management – Risk Sharing Arrangements

6.55 The submission did not propose any risk sharing arrangements (RSA). There are caps in place for pertuzumab and T-DM1. The pertuzumab cap is being consistently exceeded (by approximately [REDACTED]% in the most recent deed year), but the T-DM1 caps are not being reached. The PBAC considered that an RSA would be required to manage the uncertainties with the financial estimates, with [REDACTED]% rebates beyond estimated use. The PBAC noted that 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. To ensure the modelled cost-offsets are realised, the PBAC considered that it would be appropriate to reduce the T-DM1 and pertuzumab expenditure caps in the mBC setting. The PBAC considered the assumptions and outputs from the economic model for subsequent treatments were appropriate to determine the reduction in the mBC expenditure caps required.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of T-DM1 for the treatment of adjuvant therapy of patients with HER2 positive eBC with residual disease following HER2-targeted neoadjuvant therapy that included trastuzumab and taxane-based chemotherapy. The PBAC acknowledged the high clinical need of patients in this population. The PBAC is satisfied that T-DM1 provides, for some patients, a significant improvement in iDFS over trastuzumab. Although the data for OS were immature, the PBAC considered that there was moderate certainty that the iDFS results would translate into OS benefits based on the KATHERINE trial data. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of T-DM1 over trastuzumab was within an acceptable range.
- 7.2 The PBAC acknowledged there was a high clinical need for T-DM1 as adjuvant treatment for the requested patient group who were at a higher risk of recurrence. The PBAC acknowledged the consumer comments noting they were highly supportive of the evidence provided in the submission. The comments noted that the KATHERINE trial provided support for including T-DM1 as a new standard of care in patients with residual invasive breast cancer following neoadjuvant therapy.
- 7.3 The PBAC considered that the proposed clinical place for T-DM1 was appropriate and was consistent with the KATHERINE trial. The PBAC noted that the availability of T-DM1 in the adjuvant setting would change the treatment algorithm and improve patient outcomes. The PBAC considered that any future submissions for therapies for HER2+ eBC would need to account for the availability and efficacy of T-DM1 and demonstrate benefit in a treatment algorithm that includes T-DM1.
- 7.4 The PBAC recommended the following for the listing for T-DM1 for adjuvant treatment:
 - The PBAC agreed with the sponsor's proposed restriction that use of T-DM1 should be restricted to not more than 42 weeks (14 cycles) of combined PBS-subsidised and non-PBS-subsidised therapy in the eBC setting.
 - The initial restrictions should be Authority Required (Written) listings under the Section 100 Efficient Funding of Chemotherapy program to align with the current listings for T-DM1. The continuing restriction should be an Authority Required

(Telephone) listing under the Section 100 Efficient Funding of Chemotherapy program in order to ensure no more than the maximum number of cycles are used given the much higher cost of treatment compared to trastuzumab.

- Treatment with adjuvant T-DM1 should be restricted to patients who have undergone surgery within 12 weeks before starting T-DM1 treatment. Therefore, a clinical criterion to the effect of ‘Patient must have undergone surgery within 12 weeks within starting therapy’ should be added to the restriction.
 - Given a patient meets the criterion that they have completed neoadjuvant therapy that included trastuzumab and a taxane-based chemotherapy, HER2 status will have already been established. Therefore, the following clinical criterion does not need to be included in the initial restriction: ‘HER2 positivity must be demonstrated by in situ hybridisation (ISH)’.
 - Given there are no other anti-HER2 therapies apart from trastuzumab currently listed for adjuvant treatment of HER2 positive early breast cancer, the clinical criterion ‘The treatment must be the sole PBS-subsidised anti-HER-2 therapy’ could be removed from the restriction.
 - The PBAC considered previously that the requirement for cardiac function testing once every three months no longer contributed to determining patient eligibility for ongoing PBS-subsidised treatment with anti-HER2 therapies and advised removing this requirement was appropriate. The PBAC accepted the removal of the testing requirement from the prescribing instructions.
 - The PBAC considered it would be appropriate for grandfathered patients to access T-DM1, providing the T-DM1 had been commenced within 12 weeks of surgery, and that total non-PBS and PBS therapy was limited to 14 cycles. The PBAC noted that grandfathered patients would be eligible for treatment under the initial restriction at first, following which they would be eligible for treatment under the continuing restriction.
 - The PBAC considered it would be appropriate for patients to be allowed to switch to trastuzumab if they are unable to tolerate T-DM1. The PBAC considered a restriction flow-on to trastuzumab for early breast cancer should be applied to ensure that trastuzumab therapy does not exceed a combined duration of 52 weeks of therapy if switching from T-DM1.
- 7.5 The PBAC accepted trastuzumab as the nominated comparator on the basis that trastuzumab is the standard of care (SoC) for the adjuvant treatment of HER2+ eBC following neoadjuvant therapy.
- 7.6 The submission was based on one head-to-head randomised controlled trial (RCT), KATHERINE, comparing T-DM1 to trastuzumab. The PBAC considered that the clinical evidence provided was reliable as the KATHERINE trial was a well-conducted trial with a low risk of bias and an appropriate sample size. The PBAC considered that the clinical

data from the trial were clearly presented in the submission.

- 7.7 The primary outcome of the KATHERINE trial was iDFS. The PBAC considered that the claim that T-DM1 was superior to trastuzumab in terms of comparative effectiveness was reasonable with respect to iDFS. The PBAC considered the 50% reduction in the risk of recurrence or death in the T-DM1 treatment group, which was statistically significant in favour of T-DM1 with HR=0.50 (95% CI: 0.39, 0.64; p<0.0001), was clinically meaningful. The PBAC also noted the iDFS benefits of T-DM1 were demonstrated across different subgroups, regardless of ER status, nodal status, or whether neoadjuvant therapy comprised HER2 monotherapy (trastuzumab alone) versus doublet HER2 therapy (trastuzumab + additional HER2-directed agents).
- 7.8 The PBAC noted that OS, which was a secondary outcome, was not statistically significant (HR = 0.70 (95% CI: 0.47, 1.05)), but considered this was likely due to the immaturity of the trial data with respect to this outcome (6.6% of patients across both arms had died at the data-cut reported in the submission). The PBAC considered that a gain in OS is plausible given the strong iDFS results reported in the well-conducted trial and considered there was a moderate level of certainty around the OS benefits. However, the PBAC considered any OS gain was of uncertain magnitude given the lack of statistically significant OS results.
- 7.9 The PBAC noted that although distant recurrences overall occurred less frequently in the T-DM1 arm compared with the trastuzumab arm, a higher proportion of distant recurrences occurred in the CNS relative to other non-CNS sites in the T-DM1 arm compared with the trastuzumab arm.
- 7.10 The PBAC considered that the claim of inferior comparative safety compared with trastuzumab was reasonable. The PBAC noted that a higher incidence of AEs leading to treatment discontinuation was reported in the T-DM1 arm (n=133; 18.0%) versus the trastuzumab arm (n=15; 2.1%). However, the PBAC noted that the safety profile for T-DM1 is well documented as it is used in metastatic breast cancer and considered the AEs to be manageable. The PBAC considered that the claim of minimal impact on HRQoL was not supported by the evidence, given the higher rates of adverse events in the T-DM1 arm.
- 7.11 The PBAC noted the submission presented a stepped economic evaluation based on KATHERINE and implemented a modelled cost-utility analysis (CUA) for T-DM1 versus trastuzumab. The PBAC considered the economic model structure presented was acceptable. The PBAC considered that the economic evaluation was clearly presented in the submission.
- 7.12 The PBAC noted that the base case ICER, as proposed in the pre-PBAC response, was less than \$15,000 per QALY gained. However, the PBAC considered the 40 year time horizon used in the submission base case was not appropriate given that most women would be older than 45 years at diagnosis and because the model relied on an OS gain (extrapolated from iDFS) that was assumed to persist for 40 years despite the OS

results from the KATHERINE trial being immature and not statistically significant. The PBAC considered that greater confidence in establishing cost-effectiveness would be derived by limiting the time horizon to 20 years, and noted this resulted in an ICER that was within an acceptable range (\$15,000 per QALY).

- 7.13 The PBAC noted that a multivariate analysis was conducted using a 20-year time horizon, assuming no sustained remission adjustment and corrected transition probabilities for remission to first line mBC. The PBAC noted that for this relatively conservative multivariate analysis the ICER remained within an acceptable range (ICER of \$15,000 - \$45,000 per QALY). The PBAC noted and agreed with the other issues with the model as raised by the commentary and the ESC (as outlined in the 'Economic analysis' section), but considered that if these were corrected, the ICER would remain within an acceptable range. The sensitivity analyses indicated that the model results were reasonable and fairly robust within plausible ranges of parameters.
- 7.14 The PBAC considered that the estimated PBS population was likely overestimated in the submission. The PBAC considered the changes to the financial estimates that were proposed by the pre-PBAC response (in the scenario without neoadjuvant pertuzumab listed, which reflects the current funding situation) were reasonable, including revising the rate of HER2 targeted neoadjuvant treatment, use of neoadjuvant pertuzumab, residual disease rates and treatment uptake as outlined in Table 19.
- 7.15 The PBAC noted that cost offsets (for pertuzumab, trastuzumab and T-DM1) were included in the economic model for subsequent treatments due to a reduction in rates of metastatic disease, including within the first 6 years. However, these cost offsets were not included in the financial estimates. The PBAC considered that the clinical data in eBC and mBC indicates that most patients with recurrence would progress to second-line treatment with T-DM1 within 6 years after adjuvant therapy. The PBAC considered that cost offsets for pertuzumab, trastuzumab and T-DM1 should be included in the financial estimates consistent with the level of cost offsets estimated in the economic model.
- 7.16 The PBAC considered that there is uncertainty with regard to several assumptions applied in the financial estimates, and considered that an RSA based on the updated financial estimates with ■■■% rebate beyond the caps would be required to address these uncertainties. The PBAC noted that there are caps in place for T-DM1 and pertuzumab in the metastatic setting. As noted above, 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. To ensure the modelled cost-offsets are realised, the PBAC considered that it would be appropriate to reduce the T-DM1 and pertuzumab expenditure caps in the mBC setting in line with any amended financial estimates for T-DM1. The PBAC considered the assumptions and outputs from the economic model for subsequent treatments were appropriate to determine the reduction in the mBC expenditure caps required.

- 7.17 Under section 101(3BA) of the *National Health Act 1953*, the PBAC recommended that T-DM1 should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.18 The PBAC advised that T-DM1 is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners.
- 7.19 The PBAC recommended that the Early Supply Rule should not apply as it currently does not apply to Section 100 Efficient Funding of Chemotherapy listings.
- 7.20 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically the PBAC found that in the circumstances of its recommendation for T-DM1:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, on the basis of iDFS as outlined in paragraph 6.11;
 - b) The treatment is expected to address a high and urgent unmet clinical need in the population at high risk of disease recurrence;
 - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 7.21 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new items for new indication for trastuzumab emtansine:

Name, manner of administration	PBS item code	Max. Amount	№.of Rpts	Manufacturer
TRASTUZUMAB EMTANSINE Injection	NEW (Public) NEW (Private)	450 mg	6	
Available brands				
Kadcyla (trastuzumab emtansine 100 mg injection, 1 vial)				Roche Products Pty Ltd
Kadcyla (trastuzumab emtansine 160 mg injection, 1 vial)				

Initial treatment - Restriction Summary [new] / ToC: [new]

Concept ID	Category/Program: Section 100 – Efficient Funding of Chemotherapy; Public/Private Hospital
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	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required – Telephone/Emergency/Electronic <input type="checkbox"/> Streamlined
14726 CAR	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
24626	Administrative Advice: Increased maximum quantity will be authorised where a patient's weight is greater than 125 kg.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7754	Indication: Early HER2 positive breast cancer
	Treatment Phase: Initial adjuvant treatment
	AND
new	Clinical criteria: The treatment must commence within 12 weeks of surgery or an Authority application made within 12 weeks of surgery; OR The treatment must have commenced within 12 weeks of surgery if non-PBS subsidised treatment commenced prior to [1 Month 20XX – insert listing date here] and the patient must not have progressive disease
	AND
new	Clinical criteria: Patient must have evidence of residual invasive cancer, as demonstrated by a pathology report, in the breast and/or axillary lymph nodes following completion of surgery
	AND
new	Clinical criteria: Patient must have completed systemic neoadjuvant therapy that included trastuzumab and taxane-based chemotherapy prior to surgery
7745	Clinical criteria:
7744	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
New	Clinical criteria: Patient must not receive more than 42 weeks (14 cycles) of combined PBS-subsidised and non-PBS-subsidised therapy with this drug under both the initial and continuing adjuvant treatment restriction combined
new FULL	Prescribing Instructions: Authority applications for initial treatment must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Early Breast Cancer - PBS Supporting Information Form which includes details from the pathology report from an approved pathology authority demonstrating evidence of residual invasive carcinoma in the breast and/or axillary lymph nodes following completion of surgery.
7753 CAR	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au

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Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001
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Continuing treatment - Restriction Summary [new] / ToC: [new]

Concept ID	Category/Program: Section 100 – Efficient Funding of Chemotherapy; Public/Private Hospital
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic <input type="checkbox"/> Streamlined
24626	Administrative Advice: Increased maximum quantity will be authorised where a patient's weight is greater than 125 kg.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7754	Indication: Early HER2 positive breast cancer
	Treatment Phase: Continuing adjuvant treatment
10972	Clinical criteria:
10971	Patient must have previously been issued with an authority prescription for this drug for this condition
	AND
11485	Clinical criteria:
11484	Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug
	AND
7745	Clinical criteria:
7744	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
New (2)	Clinical criteria: Patient must not receive more than 42 weeks (14 cycles) of combined PBS-subsidised and non-PBS-subsidised therapy with this drug under the initial, grandfathering and continuing adjuvant treatment restrictions combined
14726	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

8.2 *Flow-on changes to trastuzumab emtansine in metastatic breast cancer (continuing treatment only):*

Restriction Summary 9576 / ToC: 9359: Authority Required

7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
14661	Indication: Metastatic (Stage IV) HER2 positive breast cancer
	Treatment Phase: Continuing treatment
10972	Clinical criteria:

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edit 10971	Patient must have previously been issued with an authority prescription for this drug for this condition <i>metastatic (Stage IV) HER2 positive breast cancer</i>
	AND
11485	Clinical criteria:
11484	Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug
	AND
7910	Clinical criteria:
7909	The treatment must be as monotherapy
	AND
7745	Clinical criteria:
7744	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
edit 24515	Prescribing Instructions: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. The treatment must not exceed a lifetime total of one continuous course <i>for metastatic (Stage IV) HER2 positive breast cancer</i> .
14726	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

8.3 Amend concept ID 7747 in line with the last dot-point of paragraph 7.4 of the minutes, for the following restriction summaries:

Initial treatment (weekly regimen) Restriction Summary 9355 / ToC: 9356: Authority Required: Streamlined (shown below)
 Continuing treatment (weekly regimen) Restriction Summary 9575 / ToC: 9628: Authority Required: Streamlined
 Initial treatment (3 weekly regimen) Restriction Summary 9352 / ToC: 9354: Authority Required: Streamlined
 Continuing treatment (3 weekly regimen) Restriction Summary 9572 / ToC: 9461: Authority Required: Streamlined

24626	Administrative Advice: Increased maximum quantity will be authorised where a patient's weight is greater than 125 kg.
23973 CAR	Administrative Advice: Authority applications for increased quantities/ repeats (where relevant) may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
7754	Indication: Early HER2 positive breast cancer
	Treatment Phase: Initial treatment (weekly regimen)
24648	Clinical criteria:
24647	Patient must have undergone surgery (adjuvant) or be preparing for surgery (neoadjuvant)
	AND
7745	Clinical criteria:
7744	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
7747	Clinical criteria:
edit 7746	Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy; <i>OR</i>
insert	Patient must not receive more than 52 weeks of combined trastuzumab and trastuzumab emtansine therapy if

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	adjuvant trastuzumab emtansine therapy has been discontinued due to intolerance.
7749	Prescribing Instructions: HER2 positivity must be demonstrated by in situ hybridisation (ISH).
24636	Prescribing Instructions: Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to initiating treatment with this drug for this condition.

8.4 Flow-on changes to pertuzumab in metastatic breast cancer:

Restriction Summary 9546 / ToC: 9516: Authority Required

7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
14661	Indication: Metastatic (Stage IV) HER2 positive breast cancer
	Treatment Phase: Initial treatment
14665	Clinical criteria:
14664	Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) either in the primary tumour or a metastatic lesion
	AND
10859	Clinical criteria:
10858	Patient must have a WHO performance status of 0 or 1
	AND
14667	Clinical criteria:
^{edit} 14666	Patient must not have received prior anti-HER2 therapy for this condition <i>metastatic (Stage IV) HER2 breast cancer</i>
	AND
14669	Clinical criteria:
^{edit} 14668	Patient must not have received prior chemotherapy for this condition <i>metastatic (Stage IV) HER2 breast cancer</i>
	AND
14671	Clinical criteria:
14670	The treatment must be in combination with trastuzumab and a taxane
	AND
14673	Clinical criteria:
14672	The treatment must not be in combination with nab-paclitaxel
	AND
7745	Clinical criteria:
7744	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
24514	Prescribing Instructions: Authority applications for initial treatment must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Late stage metastatic breast cancer Initial PBS authority application form which includes a copy of the pathology report from an Approved Pathology Authority confirming evidence of HER2 gene amplification in the primary tumour or a metastatic lesion by in situ hybridisation (ISH) and tick a box to state the person has Stage IV disease.
24537	Prescribing Instructions: Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval.

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7753	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
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8.5 Delete the following pertuzumab grandfathering restriction that is now more than 12 months old:

Restriction Summary 9581 / ToC: 9517: Authority Required

7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
14765	Indication: HER2 positive breast cancer
	Treatment Phase: Grandfathering treatment
14768	Clinical criteria:
14766	Patient must have previously received non-PBS subsidised treatment with this drug for this condition before 1 July 2015; or
14767	Patient must have received non-PBS subsidised trastuzumab for this condition before 1 July 2015
	AND
14770	Clinical criteria:
14769	Patient must not have received non-PBS subsidised treatment with trastuzumab for this condition before 1 July 2014
	AND
14772	Clinical criteria:
14771	Patient must not have received prior therapy with trastuzumab omtansine or lapatinib for this condition
	AND
14716	Clinical criteria:
14715	The treatment must be in combination with trastuzumab
	AND
7745	Clinical criteria:
7744	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
24511	Prescribing Instructions: Authority applications for treatment must be made in writing and must include a completed authority prescription form.
24536	Prescribing Instructions: Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA) during treatment.
7753	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services</p>

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These restrictions 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 T-DM1 for adjuvant therapy of patients with HER2 positive eBC with residual disease following HER2-targeted neoadjuvant therapy. Roche is working with the Department of Health towards a PBS listing at the earliest opportunity under Pricing Pathway A.