7.05 TUCATINIB,
Tablet 50 mg
Tablet 150mg
Tukysa®,
Pfizer Australia Pty Ltd.

1 Purpose of submission

1.1 The Standard Re-entry resubmission requested a General Schedule Section 85, Authority Required listing of tucatinib for use in combination with trastuzumab plus capecitabine for the treatment of metastatic (Stage IV) human epidermal growth factor receptor 2 positive (HER2+) breast cancer in patients who have received two prior lines of HER2-directed therapy or who have progressed on trastuzumab deruxtecan (T-DXd).

1.2 Listing was requested on the basis of a cost-utility analysis (CUA) versus trastuzumab plus capecitabine, and a cost-minimisation approach (CMA) versus trastuzumab emtansine (T-DM1).

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

Component	Description
Population	HER2+ metastatic (Stage IV) breast cancer, including patients with brain metastases. Patients are required to have received two prior anti-HER2-based regimens in the metastatic setting or in the case of patients who have progressed on T-DXd
Intervention	Tucatinib (300 mg orally twice daily) in combination with trastuzumab (6 mg/kg intravenously once every 21 days, with an initial loading dose of 8 mg/kg) and capecitabine (1000 mg / m2 of BSA orally twice daily on days 1 to 14 of each 21-day cycle)
Comparator	Trastuzumab + capecitabine T-DM1 3.6 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression
Outcomes	**Primary:** PFS **Secondary:** OS, PFS among patients with brain metastases, overall response, safety, Quality-of-life
Clinical claim	Trastuzumab + capecitabine **Efficacy:** Superiority for tucatinib in combination with trastuzumab and capecitabine vs trastuzumab and capecitabine. **Safety:** Inferior safety to trastuzumab and capecitabine, with this being regarded as tolerable and manageable T-DM1 **Efficacy:** Non-inferiority for tucatinib in combination with trastuzumab and capecitabine versus T-DM1 **Safety:** Tucatinib combination therapy has a different safety profile compared to T-DM1, with this being regarded as tolerable and manageable

Source: Table 1.1.1, p22 of the submission.
Abbreviations: BSA, body surface area; HER, human epidermal growth factor receptor 2; HER2+, HER2-positive; HER2-, HER2-negative; OS, overall survival; T-DXd, trastuzumab deruxtecan
Blue shading signifies information previously seen by the PBAC.

1.3 The key changes to the PICO compared to the previous submission were due to the Pharmaceutical Benefits Scheme (PBS) listing of T-DXd in November 2023 which is now standard of care (SOC) therapy for the treatment of HER2+ metastatic breast cancer (mBC) who have progressed following treatment with at least one prior HER2 directed regimen/s for metastatic disease, or relapsed during or within 6 months of receiving HER2 directed adjuvant therapy in Australia. This has displaced T-DM1 from a second to third-line therapy in some patients, and the submission stated that T-DM1 is now a relevant comparator in the resubmission.

2 Background

Registration status

2.1 Tucatinib was Therapeutic Goods Administration (TGA) registered on 13 August 2021 indicated 'in combination with trastuzumab and capecitabine for treatment of patients with advanced unresectable or metastatic HER2+ breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.'

Previous PBAC consideration

2.2 Tucatinib was previously considered by the Pharmaceutical Benefits Advisory Committee (PBAC) in March 2021 for the management of HER2+ mBC, including in patients with brain metastases, who (i) received one prior line of HER2-directed therapy for metastatic disease where the patient has previously received T-DM1 for either adjuvant or metastatic disease (second line mBC and adjuvant T-DM1), or (ii) who received ≥2 prior lines of HER2-directed therapy in metastatic disease (third or later line mBC).

2.3 The PBAC did not recommend the listing of tucatinib noting that while 'tucatinib provided a clinical benefit in terms of progression-free survival (PFS) and overall survival (OS) and acknowledged a high clinical need, especially in the subgroup of patients with brain metastases, [...] however, the PBAC considered that the incremental cost-effectiveness ratio (ICER) was unacceptably high at the proposed price' (paragraph 7.1, tucatinib Public Summary Document [PSD], March 2021 PBAC meeting). The PBAC also considered that the estimated number of treated patients was likely overestimated (paragraph 7.1, tucatinib PSD, March 2021 PBAC meeting).

2.4 The key changes in the resubmission for tucatinib are due to the listing of T-DXd, which was recommended by the PBAC in July 2023 as a second-line therapy for patients who have received prior anti-HER2-based regimens, subsequently displacing T-DM1 to a third line therapy.

Table 2: Summary of key matters of concern relevant to the resubmission

Component	Matters of concern (March 2021 submission)	How the resubmission addresses it
Economic evaluation – time horizon	The PBAC previously considered that for patients with mBC (and particularly those with brain metastases), a five-year time horizon would be more appropriate (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting).	The evaluation considered that this was not adequately addressed, a 10-year time horizon was still used. The resubmission argued that using a five-year time horizon would underestimate the long-term survival benefits associated with tucatinib treatment. The resubmission provided extended OS data from HER2CLIMB (observed 40% survival at 30 months – cut-off point for extrapolation). Based on the updated model extrapolations, at the end of 5 years, approximately 15.4% of patients in the tucatinib arm are still alive.
Economic evaluation – health state utility values	The PBAC previously noted the trial-based utility values were not informative as collection of QoL data was introduced to HER2CLIMB following a late protocol amendment, only 54% of patients completed the baseline questionnaire and compliance was low. In addition, the PBAC previously noted that the utility values were higher than those reported in the literature and applied in previous PBAC submissions for mBC The PBAC previously considered that utility values from Lloyd et al, 2006 were more clinically plausible (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting).	The evaluation considered that this was not adequately addressed as the HER2CLIMB utility values are still used in base case. While acknowledging that baseline assessments were only available for 54% of patients, the resubmission claimed that trial-based utilities are preferable as they capture PROs within the context of the specific treatment under evaluation. Further, the resubmission argued that Lloyd et al does not fully reflect current treatment landscapes, advancements in supportive care or improved QoL in HER2+ mBC patients receiving currently available therapies. However, the evaluation considered the Lloyd utilities were more clinically plausible.
Economic evaluation – drug costs applied in model	The PBAC previously noted that the submission did not apply a flat price per mg across the 50 mg and 150mg strengths (the cost of the 50 mg tablet was higher). The PBAC considered that a flat price per mg should be used (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting).	Addressed. A flat price per milligram for 50 mg and 150 mg was adopted in this resubmission.
Economic evaluation –RDI	The PBAC previously noted that the model assumed that all patients received 266 mg per dose (i.e., an 88.5% dose intensity was applied to a 300 mg dose). The PBAC considered that it would be more accurate to apply the distribution of doses from the trial (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting).	Addressed. The resubmission recalculated RDI based on the HER2CLIMB trial (73.5 % received the full 600 mg/day, remainder reduced monthly). The weighted average tablet use (reflecting trial distribution of 50 mg and 150 mg tablets) was applied and no wastage assumed for oral dosing.
Economic evaluation – truncation point for extrapolation	The PBAC previously noted uncertainties related to the point of extrapolation of the PFS and OS curves. The PBAC considered that K-M data should be used until approximately 20% of patients remain at risk in each arm (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting).	Addressed. The resubmission used the suggested 20% of patient's at-risk threshold to calculate the cut-off points for OS, PFS and TTD for both the all-comers patient population and the brain metastases subgroup

Component	Matters of concern (March 2021 submission)	How the resubmission addresses it
Economic evaluation – TTD curve	The PBAC previously noted the uncertainties relating to the goodness of fit of the TTD curve (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting). The ESC previously considered that it would have been more appropriate to extrapolate TTD using the log-logistic model for the tucatinib arm since it is associated with lowest AIC/BIC value (paragraph 6.47, tucatinib PSD, March 2021 PBAC meeting).	The evaluation considered that this was not adequately addressed. The resubmission argued that the log-logistic distribution overestimates the proportion of patients remaining on tucatinib relative to the TTD K-M curve, with the Gompertz curve providing the better fit (based on visual assessment).
Economic evaluation – ICER	The PBAC previously considered the ICER of $255,000 to <$355,000 per QALY was high and highly uncertain (paragraph 7.12, tucatinib PSD, March 2021 PBAC meeting). The PBAC suggested that a price reduction resulting in an ICER of $75,000 to <$95,000 per QALY should be applied (paragraph 7.17, tucatinib PSD, March 2021 PBAC meeting).	Partially addressed. The resubmission proposed revised effective AEMPs for tucatinib of $[redacted] for the 150 mg (84 tabs) (down from $[redacted] per pack) and $[redacted] for the 50 mg (88 tabs) (down from $[redacted] per pack). The base case ICER in the resubmission (vs trastuzumab plus capecitabine) was $[redacted][1]/QALY gained.
Utilisation and financial impact – patient numbers	The PBAC previously noted that the submission used a PBS 10% sample as the main source of patient estimates but considered that the sample included too few patients for it to be a reliable source for estimating the number of metastatic patients. The PBAC also considered that linear extrapolation applied to the estimated number of metastatic patients overestimated the population and that uptake rate was likely underestimated (paragraph 7.15, tucatinib PSD, March 2021 PBAC meeting). The PBAC recalled that the T-DM1 was listed on the PBS in April 2020 and considered that this listing for adjuvant disease would likely reduce the number of patients progressing to later line treatments. Therefore, the PBAC considered that the population eligible to receive tucatinib, prior to uptake rates being applied, should be no greater than that who initiated T-DM1 treatment before the adjuvant T-DM1 listing was available (i.e., April 2020) (paragraph 7.16, tucatinib PSD, March 2021 PBAC meeting).	Addressed. Utilisation estimates were based on the full PBS dataset as provided in a DUSC analysis (April 2025). The resubmission also used the number of T-DXd initiations (second line) to predict T-DXd discontinuations as the starting point for the epidemiological approach (given displacement of T-DM1 to third line with introduction of T-DXd). The evaluation considered that the uptake and the proportion continuing treatment are still uncertain and impact the estimation of utilisation.

Source: Compiled during conduction of the evaluation in part using Table 1, p14 of the submission; Table 1.1.1, p22 of the resubmission; Table 2, p56 of the resubmission; Table 1, p196-197 of the resubmission; p285-286 of the resubmission.

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CMA, cost-minimisation analysis; CUA, cost-utility analysis; DUSC, Drug Utilisation Sub Committee; ESC, Economic Sub Committee; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; KM, Kaplan-Meier; mBC, metastatic breast cancer; MBS, Medicare Benefits Schedule; mg, milligram; NMA, network meta-analysis; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PFS, progression free survival; PSD, Public Summary Document; OS, overall survival; QoL, quality of life; RDI, relative dose intensity; SPA, Special Pricing Arrangement; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTD, time to discontinuation.

The redacted values correspond to the following ranges:

[1] *$75,000 to < $95,000*

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
TUCATINIB					
tucatinib, 50 mg tablet	$4,994.36 published price $[redacted] effective price	2	176	1	Tukysa Pfizer Australia
tucatinib, 150 mg tablet	$13,998.90 published price $[redacted] effective price	2	168	1	Tukysa Pfizer Australia

Source: Table 1.4.3, p49 of the resubmission.
Abbreviations: Max, maximum; mg, milligram; №, number; PBAC, Pharmaceutical Benefits Advisory Committee; Qty, quantity; Rpts, repeats.
Note: Blue shading signifies data previously seen by the PBAC.

Category / Program: Section 85 – General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)[a]
Severity: Metastatic (Stage IV)
Condition: HER2 positive breast cancer
Indication: Metastatic (Stage IV) HER2 positive breast cancer
Treatment Phase: Initial
Clinical criteria:
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
Clinical criteria:
The condition must have progressed following treatment with at least two different HER2-directed regimens for metastatic breast cancer
OR
Clinical criteria:
The condition must have progressed following treatment with T-DXd for HER2+ metastatic breast cancer
AND
Clinical criteria:
Patient must have a WHO performance status of 0 or 1
AND
Clinical criteria:
The treatment must be in combination with trastuzumab and capecitabine

Source: Table 1.4.4, p51 of the resubmission.
Abbreviations: HER, human epidermal growth factor receptor; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.
[a] According to p50 of the resubmission, a Section 85 Telephone Authority listing is requested for initial treatment and continuing prescriptions.
Note: Blue shading signifies restrictions previously seen by the PBAC.

Category / Program: Section 85 – General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)[a]
Severity: Metastatic (Stage IV)
Condition: HER2 positive breast cancer
Indication: Metastatic (Stage IV) HER2 positive breast cancer
Treatment Phase: Continuing
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for metastatic (Stage IV) HER2 positive breast cancer
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition
AND
Clinical criteria:
Patient must be undergoing treatment with a triple drug-regimen, following issuance of this prescription, consisting of: (i) tucatinib, (ii) capecitabine, (iii) trastuzumab
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 for this PBS indication.

Source: Table 1.4.5, p52 of the resubmission.
Abbreviations: HER, human epidermal growth factor receptor; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme.
[a] According to p50 of the resubmission, a Section 85 Telephone Authority listing is requested for initial treatment and continuing prescriptions.
Note: Blue shading signifies restrictions previously seen by the PBAC.

Category / Program: Section 85 – General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (not specified)[a]
Severity: Metastatic (Stage IV)
Condition: HER2 positive breast cancer
Indication: Metastatic (Stage IV) HER2 positive breast cancer
Treatment Phase: Continuing
Clinical criteria:
Patient must have commenced treatment with this medicine for metastatic (Stage IV) HER2 positive breast cancer prior to listing date
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition
AND
Clinical criteria:
Patient must be undergoing treatment with a triple drug-regimen, following issuance of this prescription, consisting of: (i) tucatinib, (ii) capecitabine, (iii) trastuzumab

Source: Table 1.4.5, p52 of the resubmission.
Abbreviations: HER, human epidermal growth factor receptor; PBS, Pharmaceutical Benefits Scheme.
[a] The type of Authority listing requested was not specified in the resubmission.

3.1 The recommended dose of tucatinib is 300 mg twice daily continuously in combination with trastuzumab plus capecitabine. The requested maximum quantity is 168 tablets

(i.e. a maximum quantity of two packs) for the 150 mg strength and 176 tablets (i.e. a maximum quantity of two packs) for the 50 mg strength. For the 150 mg strength, this quantity corresponds with 42 days of treatment per supply at the maximum dose.

3.2 The pre-PBAC response in the previous submission for tucatinib stated that the maximum quantities for both strengths of tucatinib should correspond to 21 days of therapy (i.e., the maximum quantity should be one pack, rather than two). In March 2021, the PBAC noted that PBS listings generally supply 28 or 30 days of therapy per dispensing (paragraph 3.2, tucatinib PSD, March 2021 PBAC meeting). This was not addressed in the resubmission, which instead requested a maximum quantity of two packs for both strengths of tucatinib.

3.3 The PBAC considered that, for the 150 mg and 50 mg strengths, the maximum quantity should be one pack, noting this would provide 21 days of therapy at the maximum dose which corresponds with one treatment cycle of trastuzumab and capecitabine. Further, the PBAC considered this may reduce wastage compared with a requested maximum quantity of two packs.

3.4 The resubmission proposed a special pricing arrangement (SPA) for tucatinib, with the proposed effective ex-manufacturer price (EMP) derived using a weighted approach based on the proposed 50:50 proportion split of the two comparators (trastuzumab plus capecitabine and T-DM1 [see paragraph 5.4]) and the effective EMPs derived from the CUA and the CMA (Table 3) presented in the resubmission. As outlined in paragraphs 5.5 to 5.12, the evaluation and the ESC considered there is uncertainty regarding the proposed proportions of use between the two comparators, and whether it would be appropriate to use T-DM1 as a comparator.

Table 3: Methods used to derive the proposed effective EMP for tucatinib as presented in the resubmission and sensitivity analyses conducted during evaluation

	Tucatinib EMP
CUA derived EMP (Tucatinib vs trastuzumab + capecitabine)	50 mg: $[redacted] 150 mg: $[redacted]
CMA derived EMP (Tucatinib vs T-DM1)	50 mg: $[redacted] 150 mg: $[redacted]
Proposed effective EMP (based on 50:50 weighting of CUA and CMA price) as proposed in resubmission	**50 mg: $[redacted] 150 mg: $[redacted]**

Source: Compiled during the evaluation from Table 1.4.3, p49 of the resubmission; p198 of the resubmission.
Abbreviations: EMP, ex-manufacturer price; CMA, cost minimisation analysis; CUA, cost utility analysis; T-DM1, trastuzumab emtansine.

3.5 The resubmission requested three Authority Required restrictions for tucatinib – (i) initial treatment, (ii) continuing treatment for patients who do not have progressive disease, and (iii) grandfathering treatment for patients who have received tucatinib prior to the listing date through a patient support program and do not have progressive disease. The pre-PBAC response outlined that it would be important for the grandfather restriction to require patients to have met the prior therapy requirements in the initial listing (i.e. prior to commencement of tucatinib) given tucatinib is being investigated in earlier lines of mBC treatment. The PBAC considered

it would be appropriate to enable access for grandfather patients who otherwise met the PBS criteria at the time of initiating tucatinib.

3.6 The proposed restrictions for initial and continuing treatment closely follow the restrictions proposed in the previous submission. The key changes are:

- The clinical criterion for initial treatment now specifies that 'the condition must have progressed following treatment with at least two different HER2-directed regimens for metastatic breast cancer' OR 'the condition must have progressed following treatment with T-DXd for HER2+ metastatic breast cancer'. This was appropriate given T-DXd is now PBS-listed for metastatic patients who have progressed following prior HER2-directed therapy (or relapsed during or within 6 months of adjuvant HER2 directed treatment), displacing T-DM1 to a largely third-line setting.
- Removal of the clinical criterion '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' for both initial and continuing treatment. This was reasonable given this criterion is already included as a contraindication for trastuzumab, which is used part of the treatment regimen with tucatinib.

3.7 The restrictions, however, slightly differ from the patient population in the HER2CLIMB trial which required patients to be more heavily pretreated i.e. with pertuzumab, trastuzumab and T-DM1 (in either the neoadjuvant, adjuvant or metastatic setting), with patients in the trial having received a median of four prior lines of systemic therapy in total, and a median three prior lines of therapy in the metastatic setting.

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

4 Population and disease

4.1 HER2+ breast cancer is an aggressive subtype of breast cancer with a propensity for early relapse following adjuvant therapy. Patients with HER2+ breast cancer have an increased likelihood of lymph invasion and are likely to present with disease progression, particularly to distant metastases[1]. mBC can also affect both physical and emotional aspects of health-related quality of life (HRQoL), including pain, discomfort, anxiety and depression. Up to 50% of patients with HER2+ mBC develop brain metastases, with a demonstrated shortened survival compared to those without brain metastases[2]. There may be a clinical need for systemic HER2-targeted treatments like tucatinib that are able to cross the blood-brain barrier to target metastases in the

[1] Wang, & Xu, (2019), 'Targeted therapeutic options and future perspectives for HER2-positive breast cancer', *Signal Transduction and Targeted Therapy*, 4, 1, https://doi.org/10.1038/s41392-019-0069-2.

[2] Brufsky et al., (2011), 'Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER', Clin Cancer Res, 17, 14,

brain (while T-DXd has a clinical benefit in patients with brain metastases, it does not cross the blood-brain barrier).

4.2 The patient population targeted in this resubmission is HER2+ mBC patients, including those with brain metastases, who have either received two prior anti-HER2-based treatments in the metastatic setting or those who have progressed on T-DXd.

4.3 Tucatinib targets HER2 overexpression and mutation in tumour cells by selectively binding and inhibiting kinase domains of HER2 receptors and initiating downstream changes in the mitogen-activated protein kinase (MAPK) and protein kinase B (AKT) pathways responsible for gene regulation in processes such as cell proliferation, differentiation and survival[3]. Tucatinib has also been reported to allow penetration of the blood-brain barrier, attributed to its low molecular weight, good lipophilicity and polarity, which is important for conditions where the blood-brain barrier has not already been compromised[4].

4.4 The resubmission positioned tucatinib as a third-line treatment in the metastatic setting and/or for patients who have progressed on T-DXd. The PBAC previously considered that the place in therapy for tucatinib was appropriate (i.e., as a third- or later line treatment in patients who have progressed following treatment with at least two prior lines of HER2-directed therapy for metastatic disease (paragraph 7.3, tucatinib PSD, March 2021 PBAC meeting).

4.5 The evaluation and the ESC considered that the positioning of tucatinib was appropriate given T-DXd has since been PBS-listed for use in the metastatic setting as a: first-line therapy (for patients who have had a relapse during or within 6 months of adjuvant HER2 directed treatment); second-line therapy (for patients whose disease has progressed following treatment with one HER2-directed regimen); or third- or later-line therapy (for patients who have received more than one regimen in the metastatic setting including at least one HER2-directed regimen).

4.6 While referred to as the third-line setting throughout the submission, the proposed restriction positions tucatinib as either: third- or later-line treatment in the metastatic setting; or second-line in the metastatic setting for the subset of patients who relapsed during or within 6 months of adjuvant HER2 directed treatment and then received T-DXd in the first-line metastatic setting.

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

[3] Itani et al., (2020), 'Metastatic Presentations of Previously Treated Early-Stage Breast Cancer Patients and Association With Survival', Clinical Breast Cancer, 20, 3, https://www.sciencedirect.com/science/article/pii/S1526820919307359.

[4] Guglielmi et al., (2024), 'Targeting HER2 in breast cancer with brain metastases: A pharmacological point of view with special focus on the permeability of blood-brain barrier to targeted treatments', European Journal of Pharmacology, 985, https://www.sciencedirect.com/science/article/pii/S0014299924007660.

5 Comparator

5.1 Given the changes in the treatment landscape of HER2+ mBC as a result of PBS-listing of T-DXd, two comparators were nominated by the resubmission: (i) trastuzumab plus capecitabine, and (ii) T-DM1 monotherapy. The resubmission stated that tucatinib would replace: 'current use' of trastuzumab plus capecitabine (likely referring to use of tucatinib in patients who received T-DXd in the 3+ line setting); and 'the majority of future use of T-DM1 in this setting' (likely referring to those patients who receive T-DXd in 2L or earlier settings).

5.2 The previous submission included only trastuzumab plus capecitabine as a comparator. The PBAC previously considered that the nominated comparator of trastuzumab plus capecitabine was appropriate (paragraph 7.4, tucatinib PSD, March 2021 PBAC meeting).

5.3 The resubmission stated that discussions with Australian clinicians in the treatment of HER2+ mBC in June 2024 suggested that for patients who received T-DXd in the second line setting and whose disease will eventually progress, treatment options in third line can include either T-DM1 (that has been displaced from second to third line treatment as a result of the PBS listing of T-DXd) or trastuzumab plus capecitabine. The clinicians suggested that alternative options also include enrolment in a clinical trial.

5.4 The resubmission proposed a 50:50 proportion split of the comparators (i) trastuzumab plus capecitabine and (ii) T-DM1 based on data from the following (as outlined in Table 4):

- a sponsor-conducted online clinician survey of 30 medical oncologists in Australia (New South Wales, Victoria, Queensland and Western Australia) who had at least 3 patients in their care who were receiving T-DXd for mBC (mean of 5.8 patients receiving T-DXd per clinician), conducted in November and December 2024. Only limited additional details regarding the representativeness of the survey respondents were included (see paragraph 5.7).
- analyses of PBS data for the subsequent anti-neoplastic therapies that patients received following T-DXd between November 2023 (when T-DXd was first listed on the PBS) and April 2025 using: PBS 10% sample data (n=73); and PBS 100% data from DUSC (n=723). The PBS 10% sample was a subset of the 100% data from DUSC.

Table 4: Proportion split between trastuzumab-containing therapies and T-DM1

Source	Treatment	Proportion split (%) including all therapies	Proportion split (%) only including T-DM1 and trastuzumab-based regimens [a]
DUSC analysis (PBS 100%) [b]	Trastuzumab-based regimens	41.4%	66%
	T-DM1	20.8%	34%
	'Other' (i.e. lapatinib or chemotherapies)	38.1%	N/A
Clinician survey [c]	Trastuzumab + capecitabine	18%	23%
	T-DM1	59%	77%
	Lapatinib + capecitabine	7%	N/A
	Chemotherapy alone	2%	
	Clinical trial	11%	
	Other or BSC only	3%	
Submission's proposed comparator proportion split	**Trastuzumab + capecitabine**		**50%**
	T-DM1		**50%**

Source: Compiled during evaluation using Appendix 1.2 of resubmission, p34-37 of the resubmission.
Abbreviations: DUSC, Drug Utilisation Sub Committee; PBS. Pharmaceutical Benefits Scheme.
[a] The proportion splits from each data source were calculated during the evaluation after removal of treatment options not relevant to the resubmission.
[b] Based on utilisation data from 1 November 2023 (when T-DXd was first PBS-listed) to 15 April 2025. Note that 197 of the 820 patients (i.e. 24%) who initiated T-DXd received further treatment from medicines in ATC code L01 – Antineoplastic agents. The actual split of therapies was: 41.1% involving trastuzumab; 20.8% involving T-DM1; and 38.1% 'other' (i.e. lapatinib or chemotherapies).
[c] The resubmission stated that the clinician survey was conducted in November and December 2024 and completed by 30 medical oncologists who had at least 3 patients in their care who were receiving T-DXd for mBC (mean of 5.8 patients). Of these clinicians:

- 23 were in capital cities and 7 were regional/rural;
- 18 were public only, 4 were private only and 8 were both; and
- 6 were in NSW, 13 in Victoria, 6 in Queensland and 5 in Western Australia.

5.5 The resubmission and the Pre Sub-Committee Response (PSCR) argued that the DUSC analysis may have underestimated the utilisation of T-DM1 for the proposed patient population (i.e. skewed the results in favour of trastuzumab-containing therapies) as it included prevalent patients who received T-DM1 in the metastatic setting prior to the listing of T-DXd (i.e. patients who received T-DXd in the 3+ line setting). As such, the PSCR argued that the DUSC analysis did not capture future prescribing preferences or the evolving nature of the treatment algorithm stating 'T-DXd has displaced T-DM1 from second-line to third-line treatment, but T-DXd has a relatively long treatment duration, meaning it will take time for the PBS data to mature' (noting only 24% (197/820) of patients who initiated T-DXd since November 2023 have received a subsequent antineoplastic agent).

5.6 However, the evaluation considered that, given the PBS data reflect actual usage, the DUSC 100% analysis may be a more accurate representation of how PBS subsidised medications are currently used in clinical practice. Further, the evaluation considered that the submission may have overestimated the proportion of substitution of T-DM1 as: (a) patients who had progressive disease when treated with T-DM1 in the adjuvant setting are no longer eligible for T-DM1 in the metastatic setting; and (b) the full results of the DUSC analysis found that 38% of patients who received anti-neoplastic

therapy following T-DXd received 'other' therapies (i.e. lapatinib or chemotherapies), indicating a larger pool of patients not treated with T-DM1 subsequent to T-DXd.

5.7 The ESC noted the clinician survey was conducted across a range of settings (urban/regional and public/private), however the overall representativeness of the oncologists surveyed was unclear, declarations of potential conflicts of interest were not provided, and the response rates and range of responses were not provided. The relevant survey question was: 'What proportion of your patients who progress following treatment with T-DXd in second-line HER2+ mBC, do you anticipate you would prescribe the following available PBS-funded therapies as their third-line of treatment?' This did not account for differences in uptake of tucatinib - the ESC considered uptake of tucatinib would likely be higher from patients who would otherwise receive trastuzumab plus capecitabine (given the claim of superior efficacy) compared with uptake from patients who would otherwise receive T-DM1 (given the claim on non-inferior efficacy), thus increasing the proportion of trastuzumab plus capecitabine utilisation that would be replaced by tucatinib. Overall, the ESC considered it was unclear whether the clinician survey was sufficiently reliable to inform comparator selection.

5.8 The PSCR also presented data from the pivotal trial of T-DXd (DESTINY-Breast 03, which compared T-DXd versus T-DM1 in patients with HER2+ mBC), in which approximately half (64/130, 49%) of the patients in the T-DXd arm who received subsequent anti-cancer therapy received T-DM1.

5.9 The evaluation considered that the proposed 50:50 split used in the resubmission was uncertain and noted it has an important impact on the proposed EMP. Overall, the ESC considered that, while the DESTINY-Breast 03 trial was supportive of the proposed 50%:50% split, the proportion split remained highly uncertain.

5.10 Further, the ESC considered the weighted comparator approach was not appropriate given they do not represent different comparators for different subpopulations, that is, there are not two clinically distinct populations. The PBAC Guidelines state 'it may be appropriate to use different comparators for different subpopulations where the overall target population for the proposed medicine includes one or more sub-populations and:

- the proposed medicine is claimed to be significantly more effective or significantly less toxic than the main alternative comparator therapy in the subpopulation(s) (but not in the remainder of the target population), or,
- where the main comparator therapy used to treat the overall target population cannot be used. That therapy is, therefore, not an alternative therapy for that subpopulation' (page 14 of the Guidelines for preparing a submission to the PBAC, Version 5.0, September 2016).

5.11 Further, the ESC considered that the cost-minimisation approach versus T-DM1 was problematic because T-DM1 was recommended based on clinical evidence and a price that reflected a generally second-line mBC setting, which has limited relevance given the proposed place for tucatinib is in a generally third-line setting. Given this, the ESC

considered that a single comparator of trastuzumab plus capecitabine would be more appropriate.

5.12 In addition, the ESC noted that the DUSC analysis showed that 38% of patients received 'other' therapies (i.e. lapatinib or chemotherapies) following T-DXd, which was higher than the proportion who received T-DM1 following T-DXd (21%) in the DUSC analysis. Given the range of therapies that patients receive following T-DXd, the ESC considered that a single comparator approach would be more appropriate rather than weighting between a variety of therapies, noting the high level of uncertainty regarding the proportion of each therapy likely to be replaced (including uncertainty regarding the level of uptake of tucatinib from each of these therapies).

5.13 The pre-PBAC response maintained that tucatinib would substitute for both trastuzumab plus capecitabine and T-DM1, stating 'currently, selection of treatment is made on an individual patient basis, as there aren't any distinct subgroups of patients for whom one treatment is clearly favoured over another'. The pre-PBAC response further stated 'if listed on the PBS, tucatinib will become the new SoC in the post-T-DXd progression setting and will substitute for both trastuzumab plus capecitabine and T-DM1 in the majority of patients'. However, the PBAC considered that there was no clinical rationale for clinicians to switch patients who would otherwise be treated with T-DM1 to tucatinib. Further, the Committee considered that most patients with brain metastases would currently use trastuzumab plus capecitabine, and clinicians would likely add tucatinib onto this combination. As such, the PBAC considered that a single comparator of trastuzumab plus capecitabine was appropriate.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented the results of the HER2CLIMB trial and outlined the improved overall survival and CNS responses that were observed in patients with brain metastases. The clinician outlined that the addition of tucatinib to trastuzumab and capecitabine has manageable adverse effects (particularly given dose reductions may be used to manage adverse effects in clinical practice) and preserves quality of life. The clinician outlined the benefit of fewer Emergency Department admissions due to more effective CNS control, and also the ease of administration given it is an oral/sub-cutaneous regimen (which can be a particular advantage in patients who are working, or who live in regional/rural locations). In response to questions, the clinician outlined that tucatinib would likely be used in preference to T-DM1: in patients with brain metastases; in situations where an oral/sub-cutaneous regimen is preferred; or depending on the prior regimens received.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (5), a health care professional (1) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described the significant challenges faced by people living with metastatic HER2-positive breast cancer (third line and beyond) including pain, anxiety, fatigue and neurological symptoms, with a substantial impact on quality of life and ability to work. The comments also outlined that the condition often affects young women, and the burden it places on mothers with young children. Survival is typically limited with few treatment options after failure of more effective therapies, especially for those with brain metastases.

6.3 Input emphasised the significant clinical benefits of tucatinib in improving progression-free and overall survival, particularly for those with brain metastases. The high cost of tucatinib means many patients cannot afford it or need to make the difficult decision to access superannuation to fund treatment. The comments stated that while adverse effects are expected, they are generally manageable. Consumers identified improved survival (extending life) as the most important unmet clinical need at this stage of the condition.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for tucatinib, categorising it as one of the therapies of 'highest priority for PBS listing' on the basis of the HER2CLIMB trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for tucatinib, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement),[5] based on a comparison with trastuzumab + capecitabine.

Clinical trials

6.5 The resubmission was based on one randomised controlled trial (RCT) comparing tucatinib (in combination with trastuzumab plus capecitabine) with placebo (in combination with trastuzumab plus capecitabine in patients with HER2+ mBC who had received prior therapy for metastatic disease (N=612) (HER2CLIMB). This trial was previously considered by the PBAC in the March 2021 submission for tucatinib. The resubmission presented additional follow-up data for OS up to 29.6 months.

6.6 Following the primary analysis (previously considered by the PBAC), patients in the HER2CLIMB trial were unblinded and permitted to cross over from the placebo arm to receive tucatinib (in combination with trastuzumab plus capecitabine). The first patient crossed over in February 2020, with the resubmission presenting extended follow-up data for key secondary outcomes (OS in the 'all comers' population, PFS for the subgroup of patients with brain metastases, safety) until the final data cutoff (8

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

February 2021). Extended follow-up data from the HER2CLIMB trial following the primary analysis has not been previously considered by the PBAC. However, as the HER2CLIMB trial had already met the prespecified criteria for significance for PFS and OS in the primary analysis, prior to patient cross over, the results in the final analysis were descriptive only.

6.7 No head-to-head studies were identified that directly compared tucatinib in combination with trastuzumab plus capecitabine with T-DM1 monotherapy for HER2+ mBC. In the absence of direct comparative trials, the resubmission presented an indirect treatment comparison (ITC) of tucatinib in combination with trastuzumab plus capecitabine with T-DM1 using a network meta-analysis (NMA). The indirect comparison of tucatinib (HER2CLIMB) with T-DM1 (EMILIA [N=991]) was connected through the CEREBEL (N=540) and ELTOP (N=86) trials (which compared the relative effect between the comparators in HER2CLIMB [trastuzumab and capecitabine] and EMILIA [lapatinib + capecitabine]).

6.8 Details of the trials presented in the submission are provided in Table 5.

Table 5: Trials/studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
HER2CLIMB (NCT02614794)	Protocol number ONT-380-206 (Final Version) CSR (Primary Analysis)	30 June 2021 7 November 2019 (4 September 2019 data cutoff)
	Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis.	Annals of Oncol. 2022; 22(3):322-329
	Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2+ Metastatic Breast Cancer	N Engl J Med. 2020; 382(7):597-609
	Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial.	JAMA Oncol. 2023; 9(2):197-205
	Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2+ breast cancer with brain metastases in the HER2CLIMB Trial.	J Clin Oncol. 2020; 38(23):2610-2619
	Bachelot T, Lin NU, Murthy RK, et al. Impact of tucatinib on progression free survival in patients with HER2+ metastatic breast cancer and stable or active brain metastases. Mueller V, Wardley A, Paplomata E, et al. Preservation of quality of life in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer treated with tucatinib or placebo when added to trastuzumab and capecitabine (HER2CLIMB trial).	Annals of Oncol. 2020; 31(S4): S359-S360 Eur J Can. 2021; 153: 223e233
EMILIA (NCT00829166)	Diéras V, Miles D, Vermaet S, al. al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Verma S, Miles D, Gianni L, et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. Welslau M, Diéras V, Sohn JH, et al. Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer.	Lancet Oncol. 2017; 18(6):732-742 N Engl J Med. 2012; 367(18):1783-1791 Cancer. 2014;120(5):642-51
ELTOP (UMIN000005219)	Takano T, Tsurutani J, Takahashi M, et al. A randomized phase II trial of trastuzumab plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxanes: WJOG6110B/ELTOP	The Breast. 2018; 40: 67-75
CEREBEL (NCT00820222)	Pivot X, Manikhas A, Zurawski B, et al. CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer.	J Clin Oncol. 2015; 33(14): 1564-1573

Source: Compiled during the evaluation using Table 2.2.1, p65-66 of the resubmission, Pivot et al, 2015 and Takano et al, 2018.
Abbreviations: CSR, clinical study report; NMA, network meta-analysis; PBAC, Pharmaceutical Benefits Advisory Committee.
Blue shading indicates studies previously seen by the PBAC.

6.9 The key features of the direct randomised trial are summarised in Table 6.

Table 6: Key features of the included evidence

Trial	N	Design Duration (median FU)	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine						
HER2CLIMB	612	R, DB, MC, PC PA: 14 mo FA: 29.6 mo for OS	PA: Low FA: High	HER2+ mBC, progressed after ≥1 HER2-directed therapy	PFS, OS, ORR, PFS(BrainMets)	PFS, OS, HRQoL, safety

Source: Table 3, paragraph 6.6, tucatinib PSD, March 2021 PBAC meeting; Curigliano et al, 2022.
Abbreviations: DB, double blinded; FA, final analysis; FU, follow up; HER2+, human epidermal growth factor receptor 2-positive; HRQoL, health-related quality of life; mBC, metastatic breast cancer; MC, multicentre; ORR, overall response rate; OS, overall survival; PA, primary analysis; PBAC, Pharmaceutical Benefits Advisory Committee; PC, placebo controlled; PFS, progression-free survival; R, randomised.

6.10 The PBAC previously noted that patients with brain metastases were permitted to enrol in HER2CLIMB, including those with treated and previously untreated brain metastases. Patients with brain metastases comprised 48% of the ITT-OS population. Updated data from the exploratory analysis previously considered by the PBAC, and an additional exploratory analysis were included in the resubmission.

6.11 While the final analysis of HER2CLIMB was impacted by unblinding and cross over of patients from the placebo arm (following the primary analysis), the evaluation considered the overall risk of bias in the trial was low given: (a) the trial had already met the prespecified criteria for significance for the primary endpoint (PFS) and key secondary endpoints prior to unblinding; and (b) only a small number of patients crossed over from the placebo group (N=26 [13.2%]).

6.12 Patients enrolled in the HER2CLIMB trial were required to be treated with pertuzumab, trastuzumab and T-DM1, and thus had a median of three prior systematic therapies in the metastatic setting. Given the listing of T-DXd and subsequent displacement of T-DM1 as a third-line therapy, it is less likely that Australian patients will be pre-treated with T-DM1 (unless in the adjuvant setting). The evaluation and the ESC considered that this may reduce the applicability of the trial evidence to the proposed patient population in the resubmission.

6.13 The key features of the trials included in the ITC are summarised in Table 7.

Table 7: Key features of the included evidence – indirect comparison

Trial	N	Design Duration (median FU)	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
T-DM1 vs. lapatinib + capecitabine						
EMILIA	991	R, OL, MC PA: 12.4 mo control; 12.9 mo T-DM1 IA: 18.6 mo control; 19.1 mo T-DM1 FA: 41.9 mo control; 47.8 mo T-DM1	High	HER2+ unresectable, locally advanced breast cancer or mBC previously treated with trastuzumab and a taxane	PFS, OS	PFS, OS
Lapatinib + capecitabine vs. trastuzumab + capecitabine						
CEREBEL	540	R, OL, MC NR	High	HER2+ mBC previously treated with anthracycline and/or taxanes for (neo)adjuvant or metastatic disease	PFS, OS	PFS, OS
ELTOP	75	R, OL, MC 44.6 mo	High	HER2+ mBC previously treated with trastuzumab and taxanes	PFS, OS	PFS, OS

Source: Dieras et al, 2017; Pivot et al, 2015; Takano et al, 2018.
Abbreviations: FA, final analysis; FU, follow up; HER2+, human epidermal growth factor receptor 2-positive; HRQoL, health-related quality of life; IA, interim analysis; mBC, metastatic breast cancer; MC, multicentre; NR, not reported; OL, open label; OS, overall survival; PA, primary analysis; PC, placebo controlled; PFS, progression-free survival; R, randomised.

6.14 Overall, the evaluation considered that EMILIA, ELTOP and CEREBEL had a high risk of bias due to their open-label design. Detection bias was mitigated somewhat in EMILIA and ELTOP trials through the use of an independent review committee (IRC), masked to treatment assignment, to assess the primary endpoint of PFS (EMILIA) and incidence of brain metastases as site of first relapse (ELTOP).

6.15 There were a number of key differences across the trials that resulted in transitivity issues for the ITC, including:

- Prior therapies: HER2CLIMB reported a median number of previous therapies in the metastatic stage of 3. Although the median number of therapies were not explicitly reported in the other trials, most patients in EMILIA and ELTOP had only 0 or 1 prior lines of therapy. As such, the patient population in HER2CLIMB represents a more heavily pre-treated population.
- Presence of brain metastases: Nearly 50% of patients in HER2CLIMB had brain metastases compared to 16% in ELTOP and 0% in EMILIA (brain metastases were not reported in CEREBEL).
- Patient functional status: Approximately 50% of patients in HER2CLIMB had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, compared to 60% of patients in EMILIA and 72% of patients in ELTOP (96% of patients had an ECOG PS of 0 or 1 in CEREBEL).

6.16 Overall, the ESC noted the heterogeneity between the trials, particularly the differences in the number of lines of prior therapy (the EMILIA trial of T-DM1 was in a generally second-line mBC setting, while the HER2CLIMB trial of tucatinib was in a generally third-line or later-line setting). Overall, it was unclear whether these differences were relative treatment effect modifiers in the NMA. Further, the ESC considered there were applicability issues in terms of prior therapies as: the trials did

not include T-DXd as a prior therapy; and most patients in HER2CLIMB received prior T-DM1.

Comparative effectiveness

Direct comparison

6.17 The PBAC previously considered that the data from the HER2CLIMB trial supported the claim that the addition of tucatinib to trastuzumab and capecitabine improved PFS and OS in patients with HER2+ mBC who have previously received treatment with pertuzumab, trastuzumab and T-DM1. Statistically significant increases in overall response rate and PFS were also observed in those with brain metastases (paragraph 7.9, tucatinib PSD, March 2021 PBAC meeting).

6.18 The PBAC previously noted that tucatinib resulted in a statistically significant improvement in PFS (HR = 0.54; 95% confidence interval [CI]: 0.42, 0.71; median improvement of 2.2 months) and OS (HR = 0.66; 95% CI: 0.50, 0.88; median improvement of 4.5 months) compared to placebo (paragraph 7.7, tucatinib PSD, March 2021 PBAC meeting).

6.19 The PBAC previously noted that in patients with brain metastases, tucatinib also resulted in a statistically significant improvement in PFS (HR = 0.48; 95% CI: 0.34, 0.69; median improvement of 2.2 months) compared to placebo. The PBAC previously noted that an exploratory analysis resulted in a statistically significant improvement in OS in patients with brain metastases (HR = 0.58; 95% CI: 0.40, 0.85) (paragraph 7.8, tucatinib PSD, March 2021 PBAC meeting).

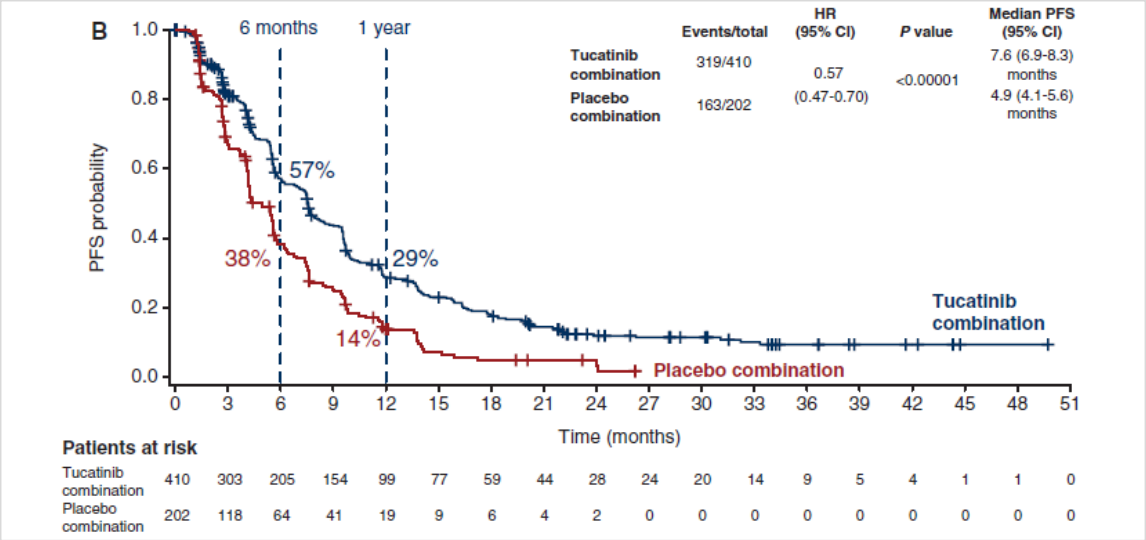
6.20 The PFS and OS results from the final analysis are presented in Table 8, Figure 1 and Figure 2. A small number of participants in the placebo arm (13%) crossed over and received treatment with tucatinib following the primary analysis in HER2CLIMB. The PFS and OS results remain consistent with those previously seen by the PBAC from the primary analysis. Additionally, sensitivity analyses that were conducted to account for patient cross over at the final analysis show that results were largely consistent with the ITT analysis with estimated OS HRs ranging from 0.71-0.72.

Table 8: Summary of key outcomes in HER2CLIMB

	Tuc+Tra+Cap	Pbo+Tra+Cap	Absolute difference	HR (95% CI)
Evidence presented in previous submission from HER2CLIMB primary analysis (04 September 2019)				
Progression-free survival per BICR (ITT-PFS population = first 480 patients randomised)				
N	320	160	-	-
Events, n (%)	178 (55.6%)	97 (60.6%)	-	-
Median PFS, months (95% CI)	7.8 (7.5, 9.6)	5.6 (4.2, 7.1)	2.2 months	**0.54 (0.42, 0.71) p< 0.00001**
% not progressed at 6 months (95% CI)	62.9% (56.9%, 68.4%)	46.3% (37.2%, 54.9%)	16.6%	-
% not progressed at 12 months (95% CI)	33.1% (26.6%, 39.7%)	12.3% (6.0%, 20.9%)	20.8%	-
Overall survival (ITT-OS population = 'all-comers' population)				
N	410	212	-	-
Deaths, n (%)	130 (31.7%)	85 (42.1%)	-	-
Median months OS (95% CI)	21.9 (18.3, 31.0)	17.4 (13.6, 19.9)	4.5 months	**0.66 (0.50, 0.88) p< 0.0048**
% alive at 12 months (95% CI)	75.5% (70.4%, 79.9%)	62.4% (54.1%, 69.5%)	13.1%	-
% alive at 24 months (95% CI)	44.9% (36.6%, 52.8%)	26.6% (15.7%, 38.7%)	18.3%	-
PFS Brainmets per BICR (ITT-PFS$_{BrainMets}$ population = 291 patients with brain metastases at baseline)				
N	198	93		
Progressed, n (%)	106 (53.5%)	51 (54.8%)	-	-
Median PFS, months (95% CI)	7.6 (6.2, 9.5)	5.4 (4.1, 5.7)	2.2 months	**0.48 (0.34, 0.69) p <0.00001**
New evidence presented in resubmission from HER2CLIMB final analysis (extended OS data) (08 February 2021)				
Progression-free survival per IA (ITT-OS population = 'all comers' population)				
N	410	212	-	-
Events, n (%)	319 (77.8%)	163 (80.7%)	-	-
Median PFS, months (95% CI)	7.6 (6.9, 8.3)	4.9 (4.1, 5.6)	2.7 months	**0.57 (0.47-0.70) p< 0.00001**
% not progressed at 6 months (95% CI)	57% (NR)[a]	38% (NR)[a]	19%	-
% not progressed at 12 months (95% CI)	29% (NR)[a]	14% (NR)[a]	15%	-
Overall survival (ITT-OS population = 'all comers' population)				
N	410	212	-	-
Deaths, n/N (%)	233 (56.8%)	137 (67.8%)	-	-
Median months OS (95% CI)	24.7 (21.6-28.9)	19.2 (16.4-21.4)	5.5 months	**0.73 (0.59-0.90) p < 0.004**
% alive at 12 months (95% CI)	75% (NR)[a]	65% (NR)[a]	10%	-
% alive at 24 months (95% CI)	51% (NR)[a]	40% (NR)[a]	9%	-

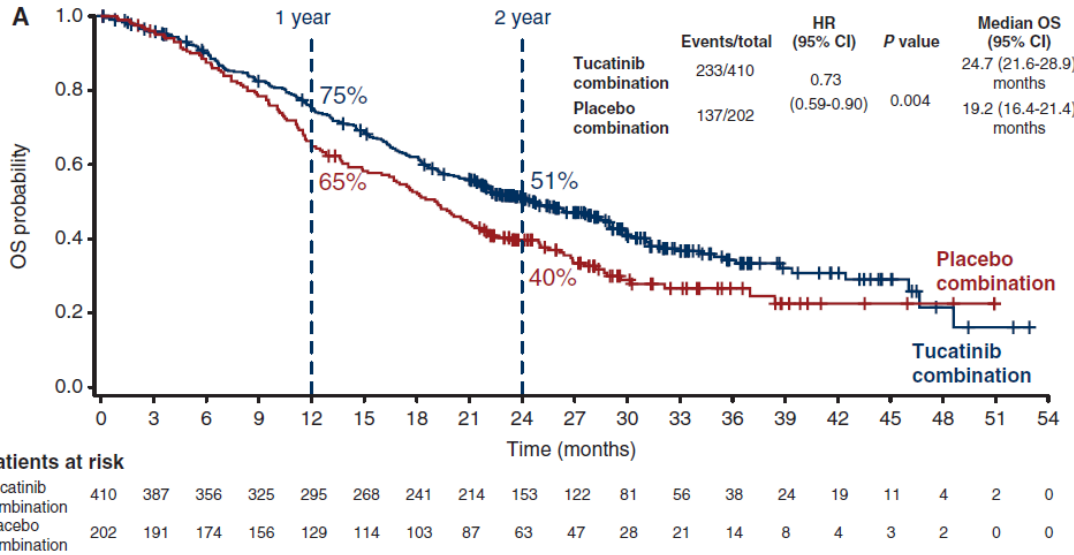
Source: Table 2.5.1, p118, Table 2.5.2, p121 & Table 2.5.6, p129 of the submission.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; HR, hazard ratio; IA, investigator assessed; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.
[a] Values obtained from the Kaplan Meier plots for PFS and OS.

Figure 1: Kaplan Meier plots of PFS in HER2CLIMB (final analysis: data cutoff 08 February 2021) – ITT-OS population (='all comers' population)



Source: Figure 2.5-1, p119 of the resubmission.
Abbreviations: BICR, blinded independent central review; Cap, capecitabine; HR, hazard ratio; IA, investigator-assessed; ITT, intention-to-treat; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; Pbo, placebo; PFS, progression-free survival; Tra, trastuzumab; Tuc, tucatinib.
Blue shading indicates data previously seen by the PBAC.

Figure 2: Kaplan Meier plots of OS in HER2CLIMB (final analysis: data cutoff 08 February 2021) – ITT-OS population (='all comers' population)



Source: Figure 2.5-3, p122 of the resubmission.
Abbreviations: Cap, capecitabine; CI, confidence interval; HR, hazard ratio; ITT intention-to-treat; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; Tra, trastuzumab; Tuc, tucatinib.
Blue shading indicates data previously seen by the PBAC.

6.21 For the subgroup of patients with brain metastases, the resubmission presented updated data from an exploratory analysis of central nervous system PFS (HR 0.39, 95% CI: 0.27, 0.56), OS (HR 0.60, 95% CI: 0.14, 0.81) and intracranial overall

response (47.3% vs 20.0%). Results from the updated subgroup exploratory analyses were consistent with those previously considered by the PBAC.

6.22 The resubmission presented an additional exploratory analysis of PFS and OS by type of brain metastases in HER2CLIMB. Patients in the tucatinib arm demonstrated a statistically significant difference in PFS for patients with stable brain metastases (HR 0.41, 95% CI 0.20, 0.85, p=0.014) and for patients with active brain metastases (HR 0.34, 95% CI 0.22, 0.54, p<0.001) as well as a statistically significant difference in OS for patients with active brain metastases (HR 0.53, 95% CI 0.36, 0.77, p<0.001).

Indirect treatment comparison

6.23 Treatment networks were constructed using relevant comparator arms from identified studies to indirectly compare PFS and OS across multiple networked clinical studies. HRs for PFS and OS were compared to assess relative differences between treatments in the network in a pairwise comparison.

6.24 A summary of PFS data from the trials in the NMA relevant to the ITC of tucatinib combination therapy with T-DM1 is presented in Table 9.

Table 9: Summary of PFS data from relevant trials in the NMA

HER2CLIMB PFS - BICR (Primary analysis 04 September 2019)				
ITT PFS population	**Tuc + Cap + Tra N=320**	**Pbo + Cap + Tra N=160**	**Hazard ratio [b] (95% CI)**	**One sided p-value**
Events, n (%) [a]	178 (55.6%)	97 (60.6%)	0.54 (0.42, 0.71)	< 0.00001
Median (95% CI), months	7.8 (7.5, 9.6)	5.6 (4.2, 7.1)		
Difference in median PFS, months	2.2			
EMILIA PFS - ICR (first interim analysis 14 Jan 2012)				
ITT population	**T-DM1 N=495**	**Lap + Cap N=496**	**Hazard ratio (95% CI)**	**One sided p-value**
Events, n (%)	265 (53.5%)	304 (61.3%)	0.65 (0.55, 0.77)	< 0.001
Median (95% CI), months	9.6 (NR)	6.4 (NR)		
Absolute difference, months	3.2			
ELTOP PFS - PFS				
ITT population	**Lap + Cap N=43**	**Tra +Cap N=43**	**Hazard ratio (90% CI)**	**Log-rank p-value**
Events, n (%)	NR	NR	0.81 (0.55, 1.21)	0.39
Median (95% CI), months	7.1 (NR, NR)	6.1 (NR, NR)		
Difference in median PFS, months	1.0			
CEREBEL PFS - Subgroup for patients previously treated with trastuzumab				
Subgroup for patients previously treated with trastuzumab	**Lap + Cap N=271**	**Tra +Cap N=269**	**Hazard ratio (95% CI)**	**Log-rank p-value**
Events, n (%)	103/167 (62%)	86/159 (54%)	1.13 (0.85, 1.50)	NR
Median (95% CI), months	6.6 (5.7, 8.3)	6.1 (5.7, 8.0)		
Difference in median PFS, months	0.5			

Source: HER2CLIMB CSR Table 14.2.4.1, p302; Verma 2012 Primary Analysis section; Takano et al (2018) Section 3.2 Efficacy; Pivot et al (2015) Efficacy outcomes & Figure 3B

Abbreviations: BICR, blinded independent central review; Cap, capecitabine; CI, confidence interval; HR, hazard ratio; ICR, blinded independent central review; ITT, intention-to-treat; Lap, lapatinib; NR, not reported Pbo, placebo; PFS, progression-free survival; T-DM1, trastuzumab emtansine; Tra, trastuzumab; Tuc, tucatinib.

Blue shading indicates data previously seen by the PBAC.

6.25 The proportional hazard assumption was significantly violated in the EMILIA trial for PFS, however results from the HR NMAs and fractional polynomial NMAs were consistent.

6.26 Results from the NMA indicate that PFS for tucatinib combination therapy was significantly better than all other treatments in the model other than T-DM1 where there was no significant difference versus tucatinib (HR, fixed effects: 0.86, 95% credible intervals (CrI) 0.60, 1.22, p=0.3973).

6.27 A summary of OS data from the trials in the NMA relevant to the ITC of tucatinib combination therapy with T-DM1 is presented in Table 10.

Table 10: Summary of OS data from relevant trials in the NMA

HER2CLIMB OS (Primary analysis 04 September 2019) – used in NMA				
ITT OS population [a]	**Tuc + Cap + Tra N=410**	**Pbo + Cap + Tra N=202**	**Hazard ratio [b] (95% CI)**	**One sided p-value**
Events, n (%)	130 (31.7)	85 (42.1)	0.66 (0.50, 0.88)	0.0048
Median (95% CI), months	21.9 (18.3, 31.0)	17.4 (13.6, 19.9)		
Difference in median OS, months	4.5			
EMILIA OS (second interim analysis)				
ITT population	**T-DM1 N=495**	**Lap + Cap N=496**	**Hazard ratio (95% CI)**	**One sided p-value**
Events, n (%)	149 (30.1)	182 (36.7)	0.68 (0.55, 0.85)	<0.001
Median (95% CI), months	30.9 (NR)	25.1 (NR)		
Difference in median OS, months	5.8			
EMILIA OS (final analysis 31 December 2014) – used in NMA				
Events, n (%)	303 (51.2)	333 (67.1)	0.75 (0.64-0.88)	NR
Median (95% CI), months	29.9 (26.3-34.1)	25.9 (22.7-28.3)		
Difference in median OS, months	4.0			
ELTOP OS				
ITT population	**Lap + Cap N=43**	**Tra +Cap N=43**	**Hazard ratio (90% CI)**	**Log-rank p-value**
Events, n (%)	NR (Not reported)	NR	0.58 (0.26, 1.31)	0.18
Median (95% CI), months	Not reached	31.0 (NR, NR)		
Difference in median OS, months	-			
CEREBEL OS				
ITT population (subgroup OS data was not available)	**Lap + Cap N=271**	**Tra +Cap N=269**	**Hazard ratio (95% CI)**	**Log-rank p-value**
Events, n (%)	70 (26)	58 (22)	1.34 (0.95, 1.90)	0.095
Median (95% CI), months	22.7 (19.5, NR)	27.3 (23.7, NR)		
Difference in median OS, months	-4.6			

Source: HER2CLIMB CSR Table 17 p. 82; Curigliano et al (2022), Figure 2A; Verma 2012 Primary Analysis section; Dieras 2017 Results section; Takano et al (2018) Section 3.2 Efficacy; Pivot et al (2015) Efficacy outcomes & Figure 2B

Abbreviations: BICR, blinded independent central review; Cap, capecitabine; CI, confidence interval; HR, hazard ratio; IA, interim analysis; ICR, blinded independent central review; ITT, intention-to-treat; Lap, lapatinib; NR, not reported Pbo, placebo; OS, overall survival; T-DM1, trastuzumab emtansine; Tra, trastuzumab; Tuc, tucatinib.

[a] Used in the NMA (noting the HER2CLIMB final analysis results were not used in the NMA)

Blue shading indicates data previously seen by the PBAC.

6.28 The NMA used OS data from the primary analysis of HER2CLIMB (prior to treatment switching in the comparator arm) and the final analysis of EMILIA (after treatment switching in the comparator arm had occurred). This resulted in the NMA using a more favourable HR for the tucatinib arm and a less favourable HR for the T-DM1 arm.

However, additional analysis using the Bucher approach using OS data from HER2CLIMB and EMILIA prior to treatment switching showed similar results to that reported in the NMA, indicating this had a limited impact.

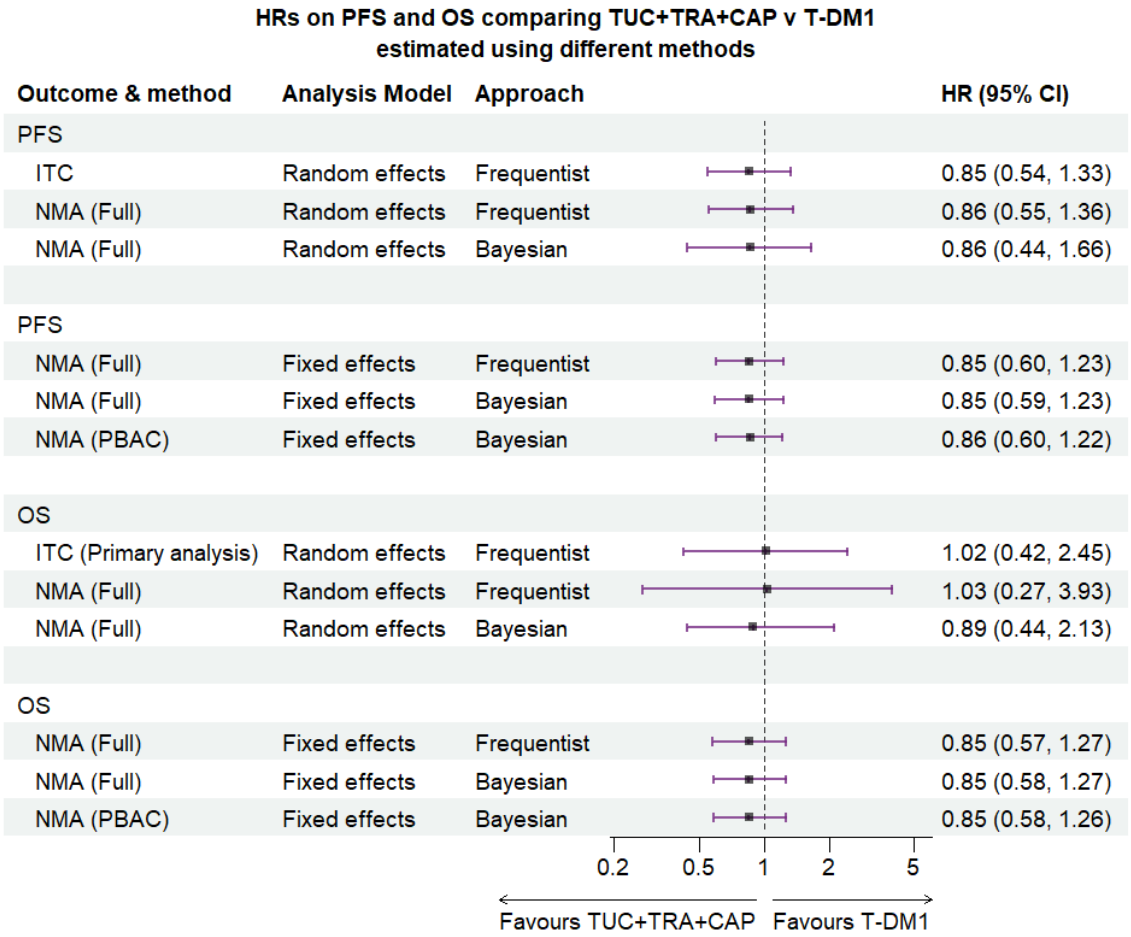
6.29 OS for tucatinib combination therapy was significantly better than all other treatments in the model other than T-DM1 which was not statistically significantly different versus tucatinib (fixed effects NMA: HR 0.85, 95% CrI 0.58, 1.26, p=0.41).

6.30 In addition to the NMA, the resubmission presented results from an ITC comparing tucatinib combination regimens to T-DM1 using an extension of the Bucher method. Transitivity issues highlighted in the NMA (paragraph 6.15) remain for the ITC.

6.31 No statistically significant differences between tucatinib (in combination with trastuzumab and capecitabine) and T-DM1 were identified using Bucher's ITC methodology. Results for OS were largely consistent in the primary analysis and sensitivity analyses.

6.32 A summary of estimates of PFS and OS HRs for the ITC of tucatinib + capecitabine + trastuzumab vs T-DM1 using different methodologies (original NMA [March 2021], PBAC NMA [February 2025] and Bucher ITCs) is presented in Figure 3. The results were generally consistent across the different approaches, noting they relied on the same trials for the common treatment pathways. The ESC considered there was uncertainty associated with the comparison between tucatinib and T-DM1 given it was based on a multi-step indirect treatment comparison/NMA which was associated with potential transitivity issues given the differences between the patient populations included in the trials (e.g. differences in the number of prior therapies, presence of brain metastases and functional status).

Figure 3: HRs for PFS and OS comparing tucatinib + capecitabine + trastuzumab vs T-DM1 estimated using different methods (NMA, Bucher ITC)



Source: Figure 2.6-8, p174 of the submission
Abbreviations: CAP, capecitabine; CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; ND, not done; NMA, Network meta-analysis; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TRA, trastuzumab; TUC, tucatinib.
Note: Full NMA (5 Mar 2021) included up to 11 treatments; PBAC relevant NMA (20 Feb 2025) included up to 7 treatments

Comparative harms

Direct comparison

6.33 A summary of the key adverse events (AEs) from the primary (data cut off 04 September 2019) and final analysis (data cut-off 8 February 2021) of HER2CLIMB are presented in Table 11. AEs from the final analysis showed no notable increase in the rates of AEs, and only one additional patient discontinued tucatinib due to an AE in the time since the primary analysis.

Table 11: Summary of key adverse events in the HER2CLIMB trial

HER2CLIMB	Tuc+Tra+Cap N=404 n (%)	Pbo+Tra+Cap N=197 n (%)	RR (95% CI)	RD (95% CI)
Any TEAE				
Primary analysis	401 (99.3%)	191 (97.0%)	1.024 (0.997, 1.051)	0.023 (0.002, 0.044)
Final analysis	401 (99.3%)	191 (97.0%)	1.024 (0.997, 1.051)	0.023 (0.002, 0.044)
≥ Grade 3 TEAE				
Primary analysis	223 (55.2%)	96 (48.7%)	1.133 (0.958, 1.340)	0.065 (-0.020, 0.150)
Final analysis	245 (60.6%)	101 (51.3%)	1.183 (1.011, 1.384)	0.094 (0.009, 0.178)
Grade ≥3 diarrhoea				
Primary analysis	52/404	17/197	1.492 (0.89, 2.51)	0.042 (-0.01, 0.09)
Final analysis	53/404	17/197	1.520 (0.91, 2.56)	0.045 (-0.01, 0.10)
Grade ≥3 hepatotoxicity				
Primary analysis	40/404	2/197	9.75 (2.38, 39.94)	0.09 (0.06, 0.12)
Final analysis	42/404	2/197	10.24 (2.50, 41.87)	0.09 (0.06, 0.13)
Any SAE				
Primary analysis	104 (25.7%)	53 (26.9%)	0.957 (0.721, 1.271)	-0.012 (-0.086, 0.063)
Final analysis	NR	NR	N/A	N/A
TEAE leading to death				
Primary analysis	8 (2.0%)	6 (3.0%)	0.650 (0.229, 1.848)	-0.011 (-0.036, 0.015)
Final analysis	6 (1.5%)	5 (2.5%)	0.585 (0.181, 1.894)	-0.011 (-0.035, 0.014)
Patients who discontinued any study treatment due to TEAE				
Primary analysis	45 (11.1%)	19 (9.6%)	1.155 (0.695, 1.920)	0.015 (-0.038, 0.067)
Final analysis	52 (12.9%)	23 (11.7%)	1.102 (0.696, 1.747)	0.012 (-0.044, 0.067)
Patients who discontinued tucatinib or placebo due to TEAE				
Primary analysis	23 (5.7%)	6 (3.0%)	1.869 (0.774, 4.516)	0.026 (-0.010, 0.063)
Final analysis	24 (5.9%)	8 (4.1%)	1.463 (0.669, 3.197)	0.019 (-0.017, 0.055)
Patients who discontinued capecitabine due to TEAE				
Primary analysis	41 (10.1%)	18 (9.1%)	1.111 (0.655, 1.882)	0.010 (-0.041, 0.061)
Final analysis	47 (11.6%)	22 (11.2%)	1.042 (0.647, 1.678)	0.005 (-0.049, 0.059)
Patients who discontinued trastuzumab due to TEAE				
Primary analysis	18 (4.5%)	5 (2.5%)	1.755 (0.661, 4.659)	0.019 (-0.014, 0.052)
Final analysis	17 (4.2%)	7 (3.6%)	1.184 (0.499, 2.809)	0.007 (-0.026, 0.039)

Source: Table 2.5.7, p132 of the resubmission; Table 6, paragraph 6.23, tucatinib PSD, March 2021 PBAC meeting; Curigliano et al, 2022.
Abbreviations: Cap, capecitabine; CI, confidence interval; PBAC, Pharmaceutical Benefits Advisory Committee; Pbo, placebo; PSD, Public Summary Document; RD, risk difference; RR, risk ratio; TEAE, treatment-emergent adverse event; Tra, trastuzumab; Tuc, tucatinib.
Blue shading indicates data previously seen by the PBAC.

6.34 The PBAC previously noted that the nature of the AEs reported in the two arms of the HER2CLIMB trial were similar, with higher rates reported in the tucatinib arm. The PBAC previously noted that the incidence of diarrhoea was significantly higher in the tucatinib arm (80.9%) as compared to the placebo arm (53.3%) and considered that prophylaxis treatment would be required (paragraph 7.10, tucatinib PSD, March 2021 PBAC meeting). Overall, the PBAC previously considered that tucatinib was inferior to placebo in terms of comparative safety (paragraph 7.11, tucatinib PSD, March 2021 PBAC meeting).

6.35 Updated safety data from the final analysis was consistent with that previously considered by the PBAC from the primary analysis; gastrointestinal toxicities (e.g., diarrhoea, nausea) and hepatoxicities (e.g., aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) of any grade were more commonly reported in the tucatinib arm. A higher proportion of Grade ≥3 treatment emergent adverse events (TEAEs) were also reported in the tucatinib arm, including palmar-plantar erythrodsaesthesia (PPE) syndrome (14% versus 9%), diarrhoea (13% vs 9%) and hepatotoxicity (10% versus 3.6%). The TEAEs reported in the trial are consistent with the side effects listed in the tucatinib Product Information (PI). Dose modifications and interruptions were used to manage these TEAEs in HER2CLIMB.

Indirect treatment comparison

6.36 To compare the safety profile of the tucatinib-based regimen with T-DM1, the resubmission presented a side-by-side analysis of TEAEs of any grade (in ≥10% of patients) and of Grade ≥3 AEs (Table 12) in the HER2CLIMB and EMILIA trials.

6.37 The tucatinib-based regimen demonstrated a greater incidence of gastrointestinal TEAEs of any grade, in particular diarrhoea (affecting nearly 82% of patients), nausea (60%) and vomiting (38%), as well as PPE syndrome (63.4% - known to be related to capecitabine use). T-DM1 demonstrated greater incidence of thrombocytopenia (31%).

6.38 For the tucatinib-based regimen, the most frequently (≥5%) reported AEs of grade ≥ 3 were PPE syndrome (14.1%), diarrhea (13.1%), increased ALT (5.7%) and fatigue (5.4%); for T-DM1, grade ≥ 3 thrombocytopenia was reported in 14.3% of patients and increased AST in 4.5% of patients.

Table 12: Summary of Grade ≥3 AEs in HER2CLIMB and EMILIA

Adverse events, n (%)	PA 04 Sep 2019	PA 14 January 2012	08 Feb 2021	31 Dec 2014
	HER2CLIMB Tuc + Cap + Tra N = 404	EMILIA T-DM1 N = 490	HER2CLIMB Tuc + Cap + Tra N = 404	EMILIA T-DM1 N = 490
Diarrhoea	52 (12.9%)	8 (1.6%)	53 (13.1%)	9 (1.8%)
Palmar-plantar erythrodsaesthesia syndrome	53 (13.1%)	0	57 (14.1%)	0
Nausea	15 (3.7%)	4 (0.8%)	16 (4.0%)	4 (0.8%)
Fatigue	19 (4.7%)	12 (2.4%)	22 (5.4%)	12 (2.4%)
Thrombocytopenia	2 (0.5)	63 (12.9%)	2 (0.5)	70 (14.3%)
Vomiting	12 (3.0%)	4 (0.8%)	13 (3.2%)	5 (1.0%)
Stomatitis	10 (2.5%)		10 (2.5%)	
Decreased appetite	2 (0.5%)		3 (0.7%)	
Headache	2 (0.5%)		3 (0.7%)	
Aspartate aminotransferase (AST) increased	18 (4.5%)	21 (4.3%)	19 (4.7%)	22 (4.5%)
Alanine aminotransferase (ALT) increased	22 (5.4%)	14 (2.9%)	23 (5.7%)	15 (3.1%)
Anaemia	17 (4.2%)	13 (2.7%)	17 (4.2%)	19 (3.9%)
Blood bilirubin increased	4 (1.0%)		4 (1.0%)	
Hypokalemia	15 (3.7)	11 (2.2%)	15 (3.7)	11 (2.2%)
Mucosal inflammation		1 (0.2%)		1 (<1%)
Neutropenia	12 (3.0)	10 (2.0%)	12 (3.0)	11 (2.2%)

Source: HER2CLIMB CSR Section 12.1 Adverse Events, Table 24 & Table 25; Curigliano 2022, Table 2
Abbreviations: AE, adverse event; Cap, capecitabine; PA, primary analysis; Pbo, placebo; Tra, trastuzumab; Tuc, tucatinib; TEAE, treatment emergent adverse event.
Green shading indicates key differences of AEs between the tucatinib and placebo arms.

Benefits/harms

6.39 A comparative benefits and harms for tucatinib (in combination with trastuzumab plus capecitabine) versus placebo and trastuzumab plus capecitabine are Table 8 and Table 11.

6.40 On the basis of the direct evidence presented by the resubmission, the comparison of tucatinib in combination with trastuzumab plus capecitabine with placebo and trastuzumab plus capecitabine over a median duration of follow-up of 29.6 months ('all comers' population) resulted in:

- Approximately 15 additional patients alive without disease progression at one year.
- Approximately 10 additional patients alive at one year.

6.41 On the basis of direct comparison evidence presented by the resubmission, for every 100 patients treated with tucatinib in combination with trastuzumab plus capecitabine in comparison with placebo and trastuzumab plus capecitabine over a median duration of exposure of 7.4 months in the tucatinib arm and 4.4 months in the comparator arm:

- Approximately 9 additional patients experienced a Grade ≥3 TEAE of any kind.

- Approximately 9 additional patients experienced severe liver damage (Grade ≥3 hepatotoxicity)
- Approximately 4 additional patients experience severe diarrhoea (Grade ≥3)

6.42 For the comparison against T-DM1, a benefits and harms table was not presented as the resubmission made a claim of non-inferiority.

Clinical claim

6.43 The resubmission described tucatinib (in combination with trastuzumab plus capecitabine) as superior in terms of effectiveness and inferior in terms of safety compared with trastuzumab plus capecitabine alone. The ESC considered that this claim was supported:

- The ESC considered that there were applicability issues with the clinical evidence given the resubmission's revised place in therapy, given patients in HER2CLIMB: did not receive prior T-DXd; and were required to have progressed on or after T-DM1, whereas prior T-DM1 therapy was no longer required in the resubmission's updated PBS restriction.
- Notwithstanding these applicability issues, the ESC considered the PBAC's previous conclusion regarding efficacy remained unchanged – i.e. the data from the HER2CLIMB trial supported the claim that the addition of tucatinib to trastuzumab and capecitabine improved PFS and OS. Statistically significant increases in overall response rate and PFS were also observed in those with brain metastases (paragraph 7.9, tucatinib PSD, March 2021 PBAC meeting).
- The resubmission presented extended PFS and OS data from the 'all comers' population in HER2CLIMB and an updated exploratory analysis for the subgroup of patients with brain metastases which continues to support for the clinical claim of superior efficacy of tucatinib (in combination with trastuzumab and capecitabine) compared to trastuzumab and capecitabine alone.
- The PBAC previously considered that tucatinib was inferior to placebo in terms of comparative safety (paragraph 7.11, tucatinib PSD, March 2021 PBAC meeting). Extended safety data from the final analysis of HER2CLIMB (data cut 8 Feb 2021) presented in the resubmission were consistent with that previously considered by the PBAC; gastrointestinal toxicities (e.g., diarrhoea, nausea) and hepatoxicities (e.g., AST and ALT) of any grade were more commonly reported in the tucatinib arm.

6.44 The PBAC considered that the claim of superior comparative effectiveness versus capecitabine and trastuzumab alone was reasonable on the basis of the HER2CLIMB trial results.

6.45 The PBAC considered that the claim of inferior comparative safety versus capecitabine plus trastuzumab alone was reasonable.

6.46 The resubmission described tucatinib (in combination with trastuzumab plus capecitabine) as non-inferior in terms of efficacy compared with T-DM1 (based on the

ITC using NMA and Bucher ITC methodologies) and having a different safety profile which was described as manageable and tolerable (based on a side-by-side analysis of TEAEs of any grade and Grade ≥3 AEs from the HER2CLIMB and EMILIA trials).

- The ESC considered that the claim of non-inferior efficacy versus T-DM1 may be reasonable but was uncertain given it was based on a multi-step indirect treatment comparison which was associated with potential transitivity issues given differences between the included trials (number of prior therapies, presence of brain metastases and functional status).
- In terms of safety, tucatinib-based regimens demonstrated a considerably greater incidence of gastrointestinal TEAEs of any grade. The evaluation and the ESC considered that the AEs associated with tucatinib-based regimens were likely to have a greater impact on HRQoL and require greater resource use for their management than those associated with T-DM1, hence the evaluation considered that a claim of inferior safety would be more appropriate. Further, the term 'manageable' was not considered to be informative. The PSCR maintained the claim of different but manageable safety, stating: 'a difference in the frequency of AEs between tucatinib combination and T-DM1 monotherapy alone [based on a side-by-side comparison] does not support a conclusion of inferior safety'. While the ESC agreed with the PSCR that it was important to consider the nature of the toxicities, the ESC considered that the Grade 3+ gastrointestinal toxicities associated with tucatinib plus trastuzumab and capecitabine (13% diarrhoea) were likely to have a greater impact on health-related quality of life than the Grade 3+ thrombocytopaenia associated with TDM-1 (13% platelets <50 $x10^9$/L), indicating that tucatinib plus trastuzumab and capecitabine was likely associated with inferior safety versus T-DM1 alone.

6.47 The PBAC considered that the claim versus T-DM1 (i.e. non-inferior effectiveness and a different but manageable/tolerable safety profile) was not relevant as the Committee did not accept that T-DM1 was a relevant comparator.

Economic analysis

6.48 The resubmission presented two economic evaluations: a CUA comparing tucatinib plus trastuzumab and capecitabine against placebo plus trastuzumab and capecitabine, similar to that considered by the PBAC at the March 2021 meeting, and a CMA comparing tucatinib plus trastuzumab and capecitabine against T-DM1, new to the resubmission due to the nomination of T-DM1 as a relevant comparator. The choice of methods is appropriate for the respective clinical claims. The proposed effective price (Table 3) for tucatinib was derived by combining results from the CUA and CMA with a 50:50 utilisation split across comparators.

Cost-utility analysis versus trastuzumab and capecitabine alone

6.49 The model structure was unchanged from the previous submission; key updates included longer OS follow-up (8 Feb 2021 cut-off), use of Kaplan Meier (K-M) data to approximately 20% at-risk point for OS, PFS and time to discontinuation (TTD),

provision of TTD K-M curves, revised handling of dose intensity and tablet pricing (flat price per mg; trial dose-distribution).

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

Component	Summary	Key changes vs March 2021 submission
Time horizon	10 years in the base case versus 29.6 months OS follow-up (133 weeks tucatinib; 117 weeks comparator) and 10.4 months PFS (48 vs 33 weeks) in trial	Time horizon unchanged; PBAC previously considered 'a five-year time horizon would be more appropriate for patients with mBC, and particularly those with brain metastases' (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting); The submission stated that a 10-year horizon was justified because 15.4% of patients remained alive at five years based on the updated OS data, and shorter horizons would underestimate long-term benefit; scenarios at 5 and 7.5 years presented.
Outcomes	LYs and QALYs	Unchanged
Methods used to generate results	Cohort partitioned survival model in Excel; weekly cycles; 5% discount rate for costs and outcomes; treatment duration from time to treatment discontinuation (TTD).	Unchanged
Health states	Progression-free; Progressed; Dead	Unchanged
Cycle length	1 week; no half-cycle correction (cycle length considered short relative to horizon).	Unchanged
Allocation to health states (partitioned survival model)	Allocation governed by PFS and OS from HER2CLIMB: PF = PFS; PD = OS − PFS; Death = 1 − OS. TTD determines time on treatment and drug costs.	Updated OS to 08 Feb 2021 cut; PFS and TTD remained at 04 Sep 2019 cut; TTD K-M (all-comers and brain-metastases) now provided; PBAC previously noted TTD K-M curves and numbers at risk were not provided (paragraph 6.47, tucatinib PSD, March 2021 PBAC meeting); TTD functions justified with external validation
Extrapolation method	K-M data used until ~20% remain at risk in each arm, then parametric extrapolation. Selection used AIC/BIC with visual and clinical plausibility. Base-case functions: OS = generalised gamma (joint model); PFS = log-logistic (joint model); TTD = Gompertz (tucatinib) and gamma (comparator). A proportional-hazards joint model was assumed for OS and PFS; no convergence or waning of effect was applied within the 10-year horizon. 54% of incremental QALYs and 63% of incremental LYs (and 4% of incremental costs) occur in the extrapolated period.	Previously switched at last K-M point (<10% at-risk). PBAC previously advised that K-M data be used until 'approximately 20% of patients remained at risk' in each arm (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting).
Health related quality of life	Trial-based EQ-5D-5L from HER2CLIMB. Applied PF utilities by cycle interval: tucatinib 0.872-0.823; comparator 0.845-0.810; PD 0.738 applied to both arms. Scenario with literature utilities (Lloyd et al., 2006: PF 0.786; PD 0.538)	Approach unchanged. PBAC previously considered it was 'not clinically plausible for patients with second- or later-line mBC to have utility values as high as 0.872'; utilities from Lloyd et al., 2006 were considered 'more clinically plausible.' (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting).

Source: Figure 3.6-1; Section 3.12.1; Tables 3.8.1-3.8.7 (Section 3.8), Figure 3.8-7; Tables 3.9.1 and 3.9.3; Table 3.10.2 and Tables 3.10.4-3.10.13 (Section 3.10) of the resubmission.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CMA, cost-minimisation analysis; CUA, cost-utility analysis; EQ-5D-5L, EuroQol 5-Dimension 5-Level; K-M, Kaplan–Meier; LYs, life-years; mBC, metastatic breast cancer; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; PD, progressed disease; PF, progression-free; PFS, progression-free survival; PSD, Public Summary Document; QALYs, quality-adjusted life-years; T-DM1, trastuzumab emtansine; TTD, time to treatment discontinuation.
Blue shading indicates these elements were unchanged from the March 2024 submission.

6.50 The evaluation and the ESC considered that there were three key model assumptions and parameter choices that were uncertain and had a substantial impact on cost-effectiveness results.

6.51 Firstly, the model retained a 10-year horizon despite the PBAC having previously considered 5 years more appropriate for third-line mBC, particularly for patients with brain metastases (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting). A 5-year horizon increased the ICER by [redacted]% to $95,000 to < $115,000 per quality adjusted life year (QALY), and 7.5 years increased it by [redacted]%. This remained a key driver of the modelled ICER. Relative to the previous submission (median OS follow-up 14.0 months), the resubmission used extended OS follow-up (median follow-up of 29.6 months; final analysis, 8 Feb 2021). However, while the additional follow-up modestly improved certainty over the first 2.5 years, the evaluation and ESC considered that it did not materially reduce uncertainty in the long-term survival extrapolations. The resubmission also provided external/real-world validation of OS and TTD against published cohorts (e.g., Kaufman et al. 2023; Anders et al. 2025); the evaluation considered that these align reasonably at 12-30 months but have limited longer term generalisability and therefore do not appear to resolve tail-of-curve uncertainty. The PSCR argued that: patients remain alive at 5 years in the model (15.4% in the tucatinib arm and 8.5% in the placebo arm in the base case); and a 5 year time horizon would be inconsistent with the PBAC's previous consideration of T-DXd in which a 15-year time horizon was used. However, the ESC noted that T-DXd is for the second-line metastatic setting rather than the third-line setting proposed for tucatinib. Overall, the ESC considered that a 7.5 year time horizon was likely appropriate to reduce uncertainty in the extrapolation of the trial data, and in the context of the third-line mBC setting. The PBAC considered that a 7.5 or 10 year time horizon would be appropriate given the resubmission had provided updated trial data compared with the previous submission, which provided greater certainty in the extrapolation.

6.52 Secondly, utilities were drawn from HER2CLIMB EQ-5D-5L with substantial missing baseline data (46% of patients did not have a baseline assessment as collection of EQ-5D data was added in a late protocol amendment), and the values appeared high. The PBAC previously considered it was not clinically plausible for patients with second- or later-line mBC to have utility values as high as 0.872, and that 'utilities derived from Lloyd et al., 2006 were considered more clinically plausible' (paragraph 7.13, tucatinib PSD, March 2021 PBAC meeting). Further, the submission applied treatment-specific utilities (i.e. higher utility values were applied in the tucatinib arm versus the placebo arm, from Cycle 5 onwards in the progression-free health state). It was unclear whether this was appropriate given tucatinib was associated with a higher rate of AEs

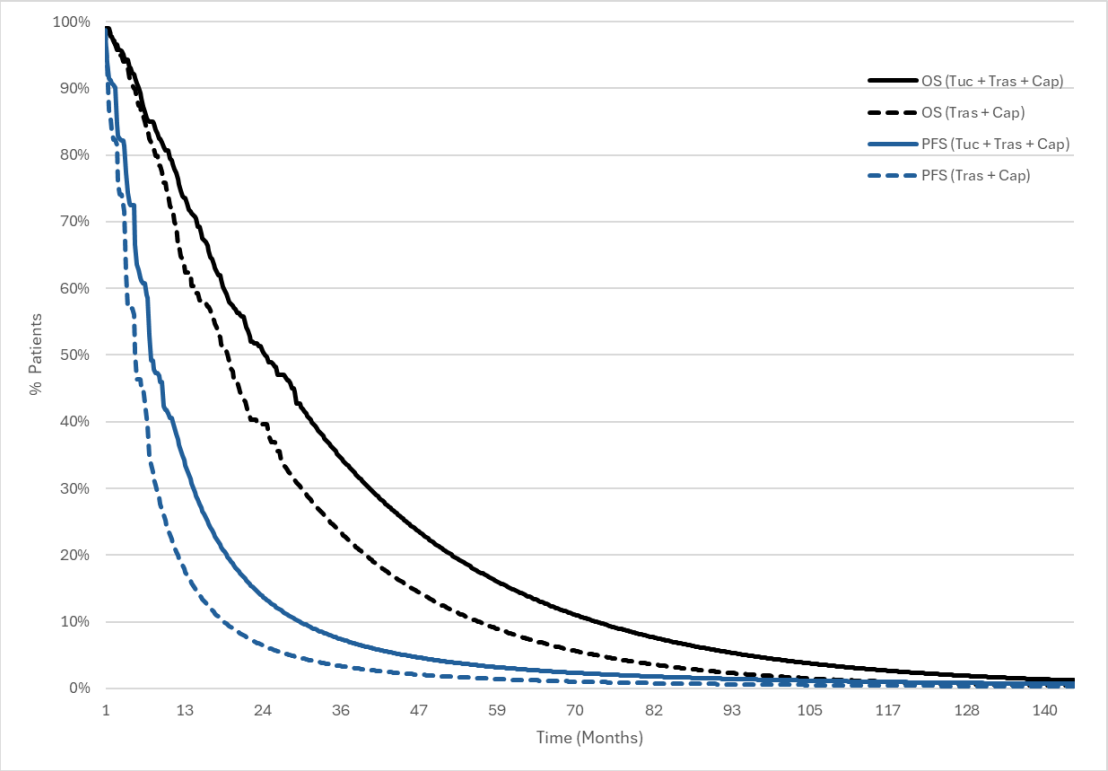
than placebo. No AE disutility was applied in the base case. Using treatment-independent Lloyd utilities in scenario analysis increased the ICER by [redacted]% to $95,000 to < $115,000 per QALY. The PSCR argued that the utility values reported in Lloyd et al. 2006 were 'based on a literature review and clinician interviews without direct patient input or validation' and 'do not reflect the current treatment landscape, advances in supportive care, or the improved quality of life experienced by patients with mBC receiving modern therapies.' The ESC noted the limitations of both Lloyd et al, 2006 and the collection of EQ-5D data in HER2CLIMB; but overall considered the trial-based utilities were implausibly high. Overall, the ESC agreed with the previous PBAC advice that the utility values derived from Lloyd et al, 2006 were more clinically plausible. However, the PBAC considered that while the utility values reported in the trial appeared high, these were preferred given the utilities from the literature (Lloyd et al, 2006) may not reflect the current treatment landscape. Further, the PBAC noted that the trial-based utilities resulted in a higher utility in the tucatinib arm versus the placebo arm from Cycle 5 onwards in the progression-free health state. The PBAC considered this may be reasonable in this case, noting the effect of tucatinib in patients with brain metastases (e.g., the potential to reduce neurological symptoms).

6.53 Thirdly, TTD for tucatinib was extrapolated using a Gompertz function rather than the statistically best-fitting log-logistic; using log-logistic increased the ICER by [redacted]% to $95,000 to < $115,000 per QALY, while Weibull or Gamma reduced it by [redacted]% each. The resubmission justified the Gompertz choice based on visual fit and external validation against real-world TTD data (Kaufman et al., 2023). However, the Gompertz function has a poorer statistical fit (fifth-ranked by AIC/BIC), and the ESC had previously preferred log-logistic (paragraph 6.47, tucatinib PSD, March 2021 PBAC meeting). The ICER is sensitive to time-on-treatment extrapolation functions. The PSCR and pre-PBAC response argued that, while the log-logistic distribution has the statistical best fit based on AIC/BIC, it is 'not clinically plausible' as 'from around 2 years onward in the tucatinib arm, the log-logistic extrapolation predicts that TTD crosses above the PFS curve.' The PSCR and pre-PBAC response argued that the log-logistic form overestimated the treatment duration, and that 'the Gompertz function is the closest and 'highest' of the remaining functions relative to the Kaplan–Meier curve'. The ESC considered the treatment duration remained uncertain. The PBAC considered that, while the Gompertz function was not the best-fitting function statistically, it may be reasonable in this case given the resubmission had externally validated it against real-world TTD data.

6.54 The model traces and extrapolations showed early separation of PFS and OS between arms consistent with HER2CLIMB, with K-M data used to the 20% at-risk point then parametric functions applied (OS generalised gamma; PFS log-logistic), as shown in Figure 4. Using the extended OS cut (08 February 2021), log-logistic remained the statistical best fit by AIC/BIC, but the resubmission selected generalised gamma on clinical-plausibility grounds (lower long-term survival); Gamma or Weibull produced more conservative long-term survival and modestly higher ICERs (+3 to 5%). The

evaluation considered Gamma/Weibull were more clinically plausible and noted limited justification for preferring generalised gamma. Only around the first 2.5 years of the 10-year horizon were informed by trial follow-up; beyond this, survival was projected by the selected parametric forms.

Figure 4: Full model trace, both treatment arms



Source: Generated during the evaluation from Model traces in tab 'PSM Trace', workbook 'Economic Model - Tuksya CEA_Section 3B_v1.0.xlsm.'.
Abbreviations: PFS, progression-free survival; OS, overall survival.

6.55 A summary of the key drivers of the model is presented in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1] /QALY gained.
Time horizon	10-year base case; PBAC's previous preference for 5 years not adopted [unchanged]	Moderate, favours tucatinib. 7.5-year horizon increased the ICER to $[redacted][1]/QALY (+[redacted]%); 5-year to $[redacted]/QALY (+[redacted]%).
Health-state utilities	Trial EQ-5D-5L values applied by cycle for PF; PD set to the minimum of the two arms; no AE disutility in base case [unchanged; Lloyd et al. 2006 used in scenario only]	High, favours tucatinib. Using treatment-independent Lloyd utilities increased the ICER to $[redacted][2]/QALY (+[redacted]%); using PD 0.538 alone increased it to $[redacted][1]/QALY (+[redacted]%).
Time to treatment discontinuation (tucatinib arm)	Gompertz chosen despite log-logistic best statistical fit; KM to 20% at risk; external TTD validation presented [cut-off revised; choice of function unchanged]	High, favours tucatinib. Using log-logistic increased the ICER to $[redacted][2] (+[redacted]%).

Source: Table 3.13.2; Table 3.12.1; Section 3.8 of the resubmission. Abbreviations: QALY, Quality-Adjusted Life Year; PBAC, Pharmaceutical Benefits Advisory Committee; ICER, Incremental Cost-Effectiveness Ratio; PF, Progression-Free; PD, Progressive Disease; AE, Adverse Event.

The redacted values correspond to the following ranges:

[1] *$75,000 to < $95,000*

[2] *$95,000 to < $115,000*

6.56 The results of the stepped economic evaluation are presented in Table 15.

Table 15: Results of the stepped economic evaluation

Step & component	Proposed medicine (tucatinib + trastuzumab + capecitabine)	Comparator (trastuzumab + capecitabine)	Increment
Step 1: trial-based costs and outcomes (29.6-month horizon)			
Costs	$[redacted]	$8,347	$[redacted]
LYs	1.74	1.55	0.19
Incremental cost/extra life year gained			$[redacted]/LY[1]
Step 2: Step 1 + costs of grade ≥3 adverse events and terminal care			
Costs	$[redacted]	$24,057	$[redacted]
LYs	1.74	1.55	0.19
Incremental cost/extra life year gained			$[redacted]/LY[1]
Step 3a: Step 2 + trial-based utilities applied to PFS only (no new costs)			
Costs	$[redacted]	$24,057	$[redacted]
QALYs	0.81	0.54	0.27
Incremental cost/extra QALY gained			$[redacted]/QALY[2]
Step 3b: Step 2 + trial-based utilities applied to total LYs (no new costs)			
Costs	$[redacted]	$24,057	$[redacted]
QALYs	1.40	1.19	0.21
Incremental cost/extra QALY gained			$[redacted]/QALY[1]
Step 4 (Base case): modelled evaluation to 10-year horizon; parametric OS/PFS extrapolation, post-progression costs; 5% discounting			
Costs	$[redacted]	$38,233	$[redacted]
QALYs	2.00	1.55	0.46
Incremental cost/extra QALY gained			$[redacted]/QALY[3]

Source: Table 3.12.1 of the resubmission.
Abbreviations: LYs, life-years; LYG, life-years gained; LY, life-year; PFS, progression-free survival; QALYs, quality-adjusted life years; QALY, quality-adjusted life year
The redacted values correspond to the following ranges:
[1] *$155,000 to < $255,000*
[2] *$115,000 to < $135,000*
[3] *$75,000 to < $95,000*

6.57 Table 16 presents the results of the brain metastases subgroup.

Table 16: Results of the economic evaluation for the brain metastases subgroup

	Proposed medicine (tucatinib + trastuzumab + capecitabine)	Comparator (trastuzumab + capecitabine)	Increment
Costs	$[redacted]	$35,519	$[redacted]
Lys	1.77	1.23	0.53
Incremental cost/extra life year gained			$[redacted][1]
QALYs	1.33	0.92	0.41
Incremental cost/QALY gained			$[redacted][2]

Source: Tables 3.12.6, p280 of the resubmission.
Abbreviations: Tuc: tucatinib; Tras: trastuzumab: Cap: Capecitabine; LYs: Life years; QALYs: Quality-adjusted life years; ICER: Incremental cost-effectiveness ratio.
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$75,000 to < $95,000*

6.58 The resubmission reported a base-case ICER of $75,000 to < $95,000/QALY for all-comers, a [redacted]% reduction from $255,000 to <$355,000/QALY in the March 2021 submission, largely driven by a lower effective EMP for tucatinib (per Table 3).

6.59 The results of key univariate and multivariate sensitivity analyses are summarised in Table 17 below. The ICER was most sensitive to treatment duration (TTD) and to the source of health-state utilities. The time horizon and OS extrapolation have smaller but still material impacts.

Table 17: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% Change in ICER from Base Case
Base case	$ [redacted]	**0.46**	$ [redacted][1]	**-**
Discount rate (base case: 5% costs and outcomes) - 0% costs and outcomes - 3.5% costs and outcomes	 $ [redacted] $ [redacted]	 0.53 0.48	 $ [redacted][2] $ [redacted][1]	 - [redacted] % - [redacted] %
Time horizon (base case: 10 years) - 5 years - 7.5 years	 $ [redacted] $ [redacted]	 0.35 0.43	 $ [redacted][3] $ [redacted][1]	 [redacted] % [redacted] %
TTD Extrapolation (Tuc + Tras + Cap) (base case: Gompertz) - Log-logistic	 $ [redacted]	 0.46	 $ [redacted][3]	 [redacted] %
PD health state utility (base case: HER2CLIMB trial EQ-5D data; 0.738) - Lloyd et al., 2006: 0.538	 $ [redacted]	 0.43	 $ [redacted][1]	 [redacted] %
Health state utility value type (base case: treatment specific from the trial) - Lloyd et al., 2006 (PFS: 0.786; PD: 0.538)	 $ [redacted]	 0.37	 $ [redacted][3]	 [redacted] %
Treatment-independent PF utilities from the trial (base case: treatment-specific) - Based on tucatinib arm: PF Cycles 1-2: 0.823; Cycles 3-4: 0.835; Cycles 5-6 0.859; Cycle 7+: 0.872. - Based on placebo arm: PF: Cycles 1-2: 0.845; Cycles 3-4: 0.835; Cycles 5-6 0.808; Cycle 7+: 0.810	 $ [redacted] $ [redacted]	 0.43 0.41	 $ [redacted][2] $ [redacted][1]	 [redacted] % [redacted] %
Multivariate analyses				
7.5-year horizon + TTD log-logistic (tucatinib arm)	$ [redacted]	0.43	$ [redacted][3]	[redacted] %
As above + treatment-independent utilities (Lloyd et al., 2006)	$ [redacted]	0.34	$ [redacted][4]	[redacted] %

Source: Table 3.13.2 of the resubmission and developed during the evaluation.
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation; PD, progressive disease; EQ-5D, EuroQol five-dimension questionnaire; K-M, Kaplan–Meier; Tuc, tucatinib; Tras, trastuzumab; Cap, capecitabine.
The redacted values correspond to the following ranges:
[1] *$75,000 to < $95,000*
[2] *$55,000 to < $75,000*
[3] *$95,000 to < $155,000*
[4] *$115,000 to < $135,000*

6.60 The ESC considered the following multivariate sensitivity analysis was informative and may represent a revised base case:

- 7.5 year time horizon;
- extrapolation of the TTD curve using the log-logistic function (tucatinib arm); and
- utilities from Lloyd et al, 2006.

The ESC noted this resulted in an ICER of $115,000 to < $135,000 per QALY. However, the PBAC considered that the resubmission's base case CUA versus trastuzumab plus capecitabine, which resulted in an ICER of $75,000 to < $95,000 per QALY, was reasonable at the CUA component price proposed in the resubmission, particularly given that a high proportion of tucatinib use will be in patients with brain metastases (refer to Section 7).

Cost-minimisation approach versus T-DM1

6.61 The PBAC considered that the claim versus T-DM1 (i.e. non-inferior effectiveness and a different but manageable/tolerable safety profile) was not relevant as the Committee did not accept that T-DM1 was a relevant comparator. Thus, the PBAC considered that the CMA versus T-DM1 was not relevant.

Weighted price

6.62 The PBAC considered that T-DM1 was not a relevant comparator, and thus the Committee considered that the weighted price was not relevant.

Tucatinib cost/patient/course

Table 18: Drug cost per patient for proposed and comparator drugs

	Proposed drug Tucatinib			Comparators					
				Capecitabine + trastuzumab			T-DM1		
	Trial dose and duration	CUA / CMA Model	Financial estimates	Trial dose and duration	CUA Model	Fin est.	Trial dose and duration	CMA Model	Financial estimates
Mean dose	531 mg/day [a]			Capecitabine 39,816 mg per 21-day cycle Trastuzumab IV 556 mg (cycle 1), 329.4 mg (cycles ≥2); SC 600 mg (cycle 1), 474.0 mg (cycles ≥2)			11.58 mg/day[a]		
Mean duration	7.6 months	CUA: 11.43 months CMA: assumed same duration as T-DM1		5.11 months	7.75 months		NR	12 months - assumed same duration as tucatinib	50 weeks (11.5 months; 16.2 admins)
Cost/ patient /month (DPMA)	$[redacted][b]	Tucatinib alone: CUA: $[redacted][b] CMA: $[redacted][b]	Weighted: $[redacted][b]	$702[b]	$687[b]		NR	$5,927[b]	$6,091[b]
Cost/ patient /course	$[redacted]	Tucatinib alone: CUA: $[redacted] CMA: $[redacted] over 11.43 months Weighted: $[redacted]	Weighted: $[redacted]	$3,583[bc]	$5,324		NR	$71,123 over 12 months (or $66,246 over 11.5 months)	$68,174 over 11.5 months

Source: Tucatinib per-cycle and course costs, dose and duration: Table 3.8.1; capecitabine and trastuzumab dose, duration and costs: Table 3.8.2; underlying inputs from Tables 1.1.4, 3.2.2, 3.10.2, 3.10.4, 3.10.5, 3.13.3, 2.4.6, 4.2.1 and 4.1.2 of the resubmission.
Abbreviations: EMP ex-manufacturer price; CMA cost-minimisation analysis; CUA cost-utility analysis; DPMA/DPMQ dispensed price for maximum amount/quantity; EMILIA T-DM1 pivotal trial; IV intravenous; NR not reported; Q3W every 3 weeks; RDI relative dose intensity; SC subcutaneous; T-DM1 trastuzumab emtansine.
[a] Mean dose calculations: tucatinib 11,151 mg per 21-day cycle / 21 = 531 mg/day (planned 600 mg/day at 88.5% RDI); T-DM1 250.2 mg per 21-day cycle × 97.22% / 21 = 11.58 mg/day.
[b] Monthly cost equals course cost divided by mean duration (months). Calculations: tucatinib trial $[redacted] / 7.6 = $[redacted]; tucatinib CUA $[redacted] / 11.43 = $[redacted] (undiscounted tucatinib costs, excluding capecitabine+trastuzumab; also aligns with tucatinib cost per 21-day cycle of $[redacted]); tucatinib CMA = $[redacted] /12; tucatinib financial $[redacted] / 11.43 = $[redacted]; capecitabine+trastuzumab trial $3,582.68 / 5.11 = $701.72; capecitabine+trastuzumab financial $5,323.86 / 7.75 = $686.95; T-DM1 CMA model $71,123 / 12 = $5,927; T-DM1 financial $4,301.73 weighted DPMA * (30.4 days per month / 21 days per cycle) = $6,091.
[c] One-year CMA horizon used for T-DM1; for Q3W dosing this is 365.25 days / 21 days = 17.39 doses.

6.63 The economic analyses (the CMA and CUA) and the financial estimates included different calculations of the RDI / compliance for tucatinib: 88.5% RDI was assumed in the economic analyses (CMA and CUA), while the financials used the distribution of doses from the trial (which resulted in an RDI of around 95%, however this was based on patients who discontinued being assumed to have full compliance, which did not seem reasonable).

Estimated PBS usage & financial implications

6.64 The resubmission used an epidemiological approach to estimate the utilisation and financial impact of listing tucatinib on the PBS/Repatriation Pharmaceutical Benefits Scheme (RPBS). The key inputs used are presented in Table 19.

Table 19: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
T-DXd PBS initiations per year	Monthly PBS data on T-DXd (items 13713R, 13718B) utilisation with prevalent, initiation and script numbers from November 2023 till March 2025	Provided by DUSC to Sponsor	This was appropriate.
Annual growth applied to initiations	2% per year	AIHW long term cancer incidence projections.	The evaluation considered that this appeared reasonable.
Rate of T-DXd discontinuations per year	1/3 cessation per year	Assumption	Adopted due to lack of a published TTD curve for T-DXd, anchored to an 18 month median duration of treatment; the evaluation considered this was reasonable but may distort the timing of patient flow into third line; the direction of effect on annual net costs was uncertain.
% of post-T-DXd patients who receive further systemic therapy	71%	DESTINY-Breast 03 (Hurvitz et al., 2023) based on % progressing to another line after T-DXd discontinuation	The resubmission used 71% to account for deaths and those not treated further; This was an important driver of the financial estimates. The ESC and PBAC considered this would likely be lower (e.g. around 60%) outside a clinical trial as real world patients are less likely to receive subsequent lines of treatment.

Data	Value	Source	Comment
Treatment utilisation for tucatinib			
Proportion of patients who currently use T-DM1 vs receive trastuzumab + capecitabine	This step/assumption was not included in the resubmission, however the PBAC considered that 50% of patients in this setting currently use T-DM1 and 50% currently use trastuzumab + capecitabine	Assumption. Generally aligns with the DUSC analysis and clinician survey (refer to Table 4).	The PBAC considered that tucatinib was likely to only be used in patients who would otherwise receive trastuzumab + capecitabine, and that this would likely represent around half the eligible population. The PBAC considered tucatinib was unlikely to be used in patients who would otherwise receive T-DM1 (i.e. negligible impact on T-DM1 usage).
Uptake % of tucatinib in eligible patients	Yr 1: [redacted]%; Yrs 2-6: [redacted]%	Assumption	This was revised from the previous submission which applied a rate of 55% in Year 1 increasing to 80% in Year 6 which was considered likely underestimated (paragraph 6.72, tucatinib PSD, March 2021 PBAC meeting). The ESC considered that the uptake rates applied in the resubmission were likely overestimated as there is now an alternative treatment in the 3L setting (i.e. T-DM1). However, the PBAC noted these uptake rates were applied across the entire eligible population i.e. regardless of whether the patient would currently receive T-DM1 or trastuzumab + capecitabine. The PBAC considered that tucatinib would likely only be used in those patients who would otherwise receive trastuzumab + capecitabine, and that uptake in this more specific population would likely be high, up to [redacted]% in Year 1 increasing to [redacted]% in Years 2 to 6.
% Continuation after initial treatment	84.6%	84.6% based on the proportion remaining progression free at Week 12 in the HER2CLIMB trial	The resubmission used PFS at 12 weeks as a proxy for continuing beyond initial supply. This appeared appropriate. No corresponding continuation assumptions were applied to T-DM1.
Mean treatment duration on tucatinib	11.43 months (~ 49.7 weeks)	Derived from the extrapolated TTD curve from the economic model.	The evaluation considered there was uncertainty around this estimate due to reliance on TTD extrapolation model, which is a sensitive modelling input. However, the PBAC considered the modelling of tucatinib TTD in the economic model was reasonable.

Data	Value	Source	Comment
Average daily dose	285.6 mg twice daily i.e. 95% of 300 mg twice daily with no missed doses	Based on the distribution of doses reported in the trial (however patients who discontinued in the trial were assumed to receive 300 mg bd doses, which did not appear plausible).	The resubmission assumed that dose reductions were accounted for in the estimation of script distribution (i.e. patients were assumed to receive a dose each day, with dose reductions reflected via dispensing lower strength scripts; skipped-dose non-adherence was not modelled separately. This resulted in an average dose of 285.6 mg (bd) i.e. 95% of 300 mg bd, which was inconsistent with the approach taken in the CUA and CMA where 88.5% RDI was assumed. Further, patients who discontinued in the trial (i.e. 5.7% of patients) were assumed to receive 300 mg bd doses, which did not appear to be appropriate. When patients who discontinued were removed from the calculations, the average dose would be 253 mg (bd) i.e. 84% of 300 mg bd; if hypothetical wastage assumptions were included (e.g. wastage of the 50 mg tablets as patients re-escalate their dose), then the RDI would likely be closer to the 88.5% assumed in the CUA and CMA. The PBAC considered that the dosing assumptions in the financial estimates should be updated to be consistent with those applied in the CUA.
Affected regimens and utilisation assumptions used for offsets			
Displacement mix for comparators	50% trastuzumab + capecitabine; 50% T-DM1.	Based on the distribution of subsequent therapies in the third line setting from the DUSC analysis of T-DXd initiations, a similar analysis using the PBS 10% dataset and a clinician survey	The evaluation considered that the proportions identified in the DUSC analysis (66% trastuzumab-involved therapies: 34%T-DM1) appear more appropriate than those identified in the clinician survey (23%: 77%). Subsequently the evaluation considered that the proposed 50:50 split used in the resubmission may not be reasonable. However, the PBAC considered that tucatinib would not displace T-DM1 i.e. tucatinib would only be added onto existing use of trastuzumab + capecitabine (thus there would be no additional costs for increased use of trastuzumab + capecitabine).

Source: Section 4 of the resubmission, the attached UCM workbook 'Tucatinib_HER2+mBC_UCM_July 2025.xlsx', DUSC PBS, clinical trial parameters, Product Information, PBS Schedule AEMPs and MBS fee schedule as specified in the 'Source' column.

Abbreviations: 3-L, third-line; AE, adverse event(s); AEMP, Approved Ex-Manufacturer Price; AEMPs, Approved Ex-Manufacturer Prices; AIHW, Australian Institute of Health and Welfare; BID, twice daily; CMA, cost minimisation analysis; DPMQ, Dispensed Price for Maximum Quantity; DPMQs, Dispensed Prices for Maximum Quantity; DUSC, Drug Utilisation Sub Committee; DoT, duration of treatment; IV, intravenous; KM, Kaplan–Meier; MBS, Medicare Benefits Schedule; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PFS, progression-free survival; PI, Product Information; Q4, fourth quarter; RDI, relative dose intensity; RDIs, relative dose intensities; RPBS, Repatriation Pharmaceutical Benefits Scheme; SC, subcutaneous; SPA, special pricing arrangement; TTD, time to treatment discontinuation; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; UCM, Utilisation and Cost Model; Yr, year.

6.65 Table 20 presents the net financial implications presented in the resubmission.

Table 20: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of tucatinib						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to PBS/RPBS/MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Previous submission (March, 2021)						
Net cost to PBS/RPBS	$[redacted]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][6]

Source: Table 4.2.2; 4.2.3; 4.2.6; 4.2.8; 4.3.3; 4.4.1; 4.5.2; 4.5.3 of the resubmission; Table 4.8 of the March 2021 submission.
Abbreviations: MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.
[a] Assuming approximately 7.8 scripts per patient per year (Year 1 approximately 7.5) as estimated by the resubmission.
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5,000*
[3] *$10 million to < $20 million*
[4] *$0 to < $10 million*
[5] *$20 million to < $30 million*
[5] *$30 million to < $40 million*

6.66 The resubmission estimated a net PBS/RPBS impact of $0 to < $10 million in Year 1, rising to $0 to < $10 million in Year 6, totalling $20 million to < $30 million over six years.

6.67 The resubmission's financial estimates applied the weighted price and assumed a 50:50 split of comparators between (i) T-DM1 (with offsets for reduced use of T-DM1 and costs for increased use of trastuzumab plus capecitabine) and (ii) trastuzumab plus capecitabine alone. The evaluation noted that:

- When 100% CMA was assumed (including use of the indication-specific tucatinib price from the CMA and offsets for T-MD1), the listing was approximately cost-neutral (cost of around $[redacted] per patient) for those patients who continue. However, the financial estimates assumed that 15.4% of patients would discontinue tucatinib after 12 weeks, while no discontinuation assumptions were applied for T-DM1. For those patients that discontinue, the financials estimated a

net saving of around $0 to < $10 million per patient. However, the PBAC considered that the CMA was not relevant.

- With only the CUA assumptions applied (including use of the resubmission's proposed indication-specific tucatinib price from the CUA), the net cost to the PBS/RPBS per patient was around $0 to < $10 million.

6.68 The PBAC considered that tucatinib was likely to only replace trastuzumab plus capecitabine, and that this would likely represent around half the estimated third-line population. That is, of the patients who progress on T-DXd and receive further treatment, the PBAC considered that half would currently use T-DM1 and half would use trastuzumab + capecitabine. The PBAC considered tucatinib was unlikely to be used in patients who would otherwise receive T-DM1 (i.e. negligible impact on T-DM1 usage).

6.69 The evaluation and the ESC considered that the accuracy of the utilisation and financial estimates was limited by several key uncertainties:

- Time on treatment was based on the extrapolated TTD curve from the economic model which was uncertain (refer to paragraph 6.53). The modelled tucatinib mean duration of treatment was 11.43 months (about 49.7 weeks) extrapolated from the HER2CLIMB trial. However, the PBAC considered the modelling of tucatinib TTD in the economic model was reasonable.
- The financial estimates assumed a 12-week continuation rate of 84.6% (based on the PFS at 12 weeks). No corresponding continuation assumptions were applied to T-DM1, and the PSCR acknowledged that it may be appropriate to apply a discontinuation rate for T-DM1 consistent with the discontinuation rate applied to tucatinib in the utilisation estimates. The PBAC considered that the T-DM1 discontinuation rates were not relevant as tucatinib was unlikely to displace T-DM1.
- The resubmission assumed that one-third of patients would discontinue T-DXd each year and that 71% of these patients would receive further systemic treatment (to account for deaths and patient who do not receive further treatment). The latter (71%) was based on the DESTINY-Breast 03 trial of T-DXd (i.e. the proportion of patients who progressed to another line after T-DXd discontinuation). The ESC and the PBAC considered this proportion would likely be lower (e.g. around 60%) as real world patients are generally less fit than patients enrolled in a clinical trial and thus, in clinical practice, fewer patients are likely to receive the next line of treatment.
- The resubmission assumed uptake rates of [redacted]% in Year 1 increasing to [redacted]% in Year 2, which the evaluation and the ESC considered may be overestimated. While the PBAC had previously considered that the uptake rates applied in the March 2021 submission ([redacted]% in Year 1 increasing to [redacted]% in Year 6) were likely underestimated; the ESC considered that the higher rates applied in the resubmission had now likely overestimated uptake given there is now an alternative treatment in the 3L setting (i.e. T-DM1). However, the PBAC

noted these uptake rates were applied across the entire eligible population i.e. regardless of whether the patient would currently receive T-DM1 or trastuzumab + capecitabine. The PBAC considered that tucatinib would likely only be used in patients who would otherwise receive trastuzumab plus capecitabine, and that uptake in this more specific population would likely be high, up to [redacted]% in Year 1 increasing to [redacted]% in Years 2 to 6.

Quality Use of Medicines

6.70 The resubmission stated that the Sponsor would support quality use of medicines by providing educational materials for health professionals (PI, safety and efficacy information, Patient Management Guide and Therapeutic Guide), patient-facing Consumer Medicine Information and a patient information booklet, engaging with Breast Cancer Network Australia, and updating the PSUR in line with TGA requirements.

Financial Management – Risk Sharing Arrangements

6.71 The resubmission did not propose any risk sharing arrangements. However, the PBAC considered that an RSA may be required.

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

7 PBAC Outcome

7.1 The PBAC recommended tucatinib for use in combination with trastuzumab plus capecitabine for the treatment of metastatic (Stage IV) human epidermal growth factor receptor 2 positive (HER2+) breast cancer in patients who have received at least two prior lines of HER2-directed therapy or who have progressed on trastuzumab deruxtecan (T-DXd). The PBAC recognised the clinical need for additional treatment options in this later-line setting particularly for patients with brain metastases, and noted that tucatinib improves overall survival compared with trastuzumab plus capecitabine alone. The PBAC considered tucatinib would be acceptably cost-effective at the cost-utility analysis (CUA) component price proposed, based on the resubmission's base case CUA versus trastuzumab plus capecitabine. However, the PBAC did not accept the resubmission's claim that tucatinib would also replace trastuzumab emtansine (T-DM1) and thus considered the cost-minimisation component of the proposed weighted price was not relevant. The PBAC considered that the financial estimates including the cost per patient should be based on tucatinib replacing trastuzumab plus capecitabine only.

7.2 The PBAC was satisfied that tucatinib in combination with trastuzumab plus capecitabine provides, for some patients, a significant improvement in efficacy over trastuzumab plus capecitabine alone.

7.3 The PBAC welcomed the consumer input received from individuals, organisations and a health professional which described the significant challenges faced by people living with metastatic HER2-positive breast cancer (third- or later-line and beyond) including pain, anxiety, fatigue and neurological symptoms, with a substantial impact on quality of life and ability to work. Consumers identified improved survival (extending life) as the most important unmet clinical need at this stage of the condition. The PBAC considered that, while multiple lines of treatment are available on the PBS, there is a high clinical need for effective treatments in later-lines for patients with brain metastases, where current options have limited efficacy.

7.4 The resubmission positioned tucatinib as a third- or later-line treatment in the metastatic setting and/or for patients who have progressed on T-DXd. The PBAC considered this was reasonable, and noted that the addition of T-DXd to the PBS since the previous submission has shifted the treatment landscape, i.e. T-DXd is now listed in the second- or later-line metastatic setting (or in the first-line metastatic setting for patients who have relapsed during or within 6 months of adjuvant HER-2 directed treatment). This has displaced trastuzumab emtansine (T-DM1) from second-line to third-line.

7.5 The PBAC noted that the resubmission proposed a 50:50 proportion split between two comparators: (i) trastuzumab plus capecitabine; and (ii) T-DM1. However, the PBAC considered that tucatinib will almost exclusively be added to trastuzumab plus capecitabine, with negligible impact on T-DM1 usage. In particular, the Committee considered that most patients with brain metastases would currently use trastuzumab plus capecitabine, and clinicians would likely add tucatinib onto this combination. The PBAC considered that there was no clinical rationale for replacing T-DM1 with tucatinib (plus capecitabine and trastuzumab) as tucatinib (plus capecitabine and trastuzumab) does not provide an efficacy or safety advantage over T-DM1. As such, the PBAC considered that a single comparator of trastuzumab plus capecitabine was appropriate.

7.6 The PBAC accepted the claim that tucatinib (plus capecitabine and trastuzumab) has superior comparative effectiveness versus capecitabine plus trastuzumab alone, based on the HER2CLIMB trial. The PBAC noted that the final analysis of HER2CLIMB reported a PFS HR of 0.57 (95% CI: 0.47, 0.70), and an OS HR of 0.73 (95% CI: 0.59, 0.90) in the ITT population, which was consistent with the results previously seen by the PBAC for the primary analysis. For the subgroup of patients with brain metastases, the resubmission presented updated data from an exploratory analysis of central nervous system PFS (HR: 0.39; 95% CI: 0.27, 0.56) and OS (HR: 0.60; 95% CI: 0.14, 0.81).

7.7 The PBAC considered that the recent addition of T-DXd to the treatment algorithm introduced applicability issues as patients in HER2CLIMB: were required to have received prior T-DM1 (though this was no longer required in the resubmission's proposed restriction); and did not receive prior T-DXd (though patients in clinical practice are likely to have received prior T-DXd). Notwithstanding this issue, the PBAC

considered the results of the HER2CLIMB trial demonstrated a clinically meaningful survival benefit, and a clear benefit in patients with brain metastases.

7.8 In terms of safety, the PBAC considered that tucatinib plus capecitabine plus trastuzumab has inferior safety compared with capecitabine plus trastuzumab alone, primarily due to increased rates of Grade 3+ gastrointestinal toxicity (with rates of Grade ≥3 diarrhoea of 13% versus 9%, respectively).

7.9 The PBAC considered that the clinical claim versus T-DM1 (i.e. non-inferior effectiveness and a different but manageable/tolerable safety profile) was not relevant as the Committee did not accept that T-DM1 was a relevant comparator. Thus, the PBAC considered that the CMA versus T-DM1 was not relevant.

7.10 For the cost-utility analysis (CUA) versus trastuzumab plus capecitabine, the PBAC noted that the evaluation and the ESC had considered that the following key concerns raised by the PBAC in March 2021 remained outstanding:

- The resubmission applied a 10-year horizon despite the PBAC previously considering that 5 years would be more appropriate. The PBAC considered that, in the context of the resubmission, a 7.5 or 10 year time horizon would be appropriate given the updated trial data which provided greater certainty in the extrapolation. The PBAC noted that a 7.5 year time horizon would increase the ICER by [redacted]% from $75,000 to < $95,000 per quality-adjusted life year (QALY) to $75,000 to < $95,000/QALY.
- Utilities continued to be derived from the HER2CLIMB trial EQ-5D data. This was despite the PBAC previously considering that values from the literature (i.e. from Lloyd et al, 2006) would be more appropriate given there were issues with the trial-based data, notably there were substantial missing baseline data and the resulting utility values appeared high. However, the PBAC considered that, while the utility values derived from HER2CLIMB appeared high, these were preferred given the utilities from the literature (Lloyd et al, 2006) may not reflect the current treatment landscape. Further, the PBAC noted that the trial-based utilities resulted in a higher utility in the tucatinib arm versus the placebo arm from Cycle 5 onwards in the progression-free health state. The PBAC considered this may be reasonable in this case, noting the effect of tucatinib in patients with brain metastases (e.g. the potential to reduce neurological symptoms).
- Time on treatment for tucatinib was extrapolated using the Gompertz function rather than the statistically best-fitting log-logistic function. However, the PBAC considered that it may be reasonable to use the Gompertz function in this case given the resubmission had externally validated the extrapolation results against real-world TTD data.

7.11 The PBAC considered that the resubmission's base case CUA versus trastuzumab plus capecitabine, which resulted in an ICER of $75,000 to < $95,000 per QALY, was reasonable at the CUA component price proposed in the resubmission. The PBAC noted this price was lower than the weighted price proposed in the resubmission

(because the weighted price included costs derived from the CMA, which the PBAC did not consider to be relevant). Overall, the PBAC considered that a reduction in treatment costs would be required to achieve the ICER proposed in the resubmission (i.e. an ICER of $75,000 to < $95,000/QALY in the sponsor's proposed base case) and noted this would result in tucatinib drug costs of around $[redacted] per patient (tucatinib drug costs only, undiscounted).

7.12 The PBAC considered the key issue with the financial estimates was the resubmission's assumption that tucatinib would replace T-DM1. The PBAC considered the following would be more appropriate:

- tucatinib replacing trastuzumab plus capecitabine only, and that this would likely represent around half the estimated third line population. That is, of the patients who progress on T-DXd and receive further treatment, the PBAC considered that half would currently use T-DM1 (and this cohort were unlikely to receive tucatinib) and half would use trastuzumab plus capecitabine.
- uptake in patients who would otherwise use trastuzumab plus capecitabine would likely be high, up to [redacted]% in Year 1, increasing to [redacted]% in Years 2–6.
- the PBAC agreed with ESC that the proportion of patients who discontinue T-DXd and receive further systemic treatment (71%) was likely overestimated by the resubmission. The PBAC considered this proportion would likely be lower (e.g., around 60%) as real world patients are generally less fit than patients enrolled in a clinical trial and thus, in clinical practice, fewer patients are likely to receive the next line of treatment.
- the PBAC considered that the dosing assumptions in the financial estimates should be updated to be consistent with those applied in the CUA.

7.13 The PBAC considered that, with these adjustments applied to the financial estimates, there would be a reasonably high level of certainty in the financial estimates.

7.14 The PBAC considered that an RSA may be appropriate if there is a risk of the cost per patient exceeding that outlined in paragraph 7.11. In this circumstance, the PBAC considered that [redacted]% reimbursement would be required for expenditure above the utilisation estimates (i.e. based on the resubmission's utilisation estimates, adjusted for the issues outlined in paragraph 7.12, and based on the treatment costs outlined in paragraph 7.11).

Restriction

7.15 The PBAC considered that an Authority Required (Streamlined) listing would be appropriate for tucatinib, consistent with the existing listing for trastuzumab.

7.16 The PBAC considered that, for the 150 mg and 50 mg strengths, the maximum quantity should be one pack for both the initial and continuing listings, noting this would provide 21 days of therapy (with the 150 mg strength) at the maximum dose, which corresponds with one treatment cycle of trastuzumab and capecitabine. The PBAC considered this may reduce wastage compared with the requested maximum quantity

of two packs.

7.17 The PBAC considered that the maximum number of repeats should be: two for the 150 mg strength; and one for the 50 mg strength (for both the initial and continuing listings). This would allow nine weeks of treatment with the initial listing at the maximum dose (300 mg twice daily). The lower number of repeats for the 50 mg strength reflects the potential for excess supply (e.g., if doses fluctuate or if a stable dose of 200 mg dose is prescribed), but with a direction to Services Australia that an increase in the number of repeats is permitted if required.

7.18 The resubmission requested a grandfather restriction for patients who received tucatinib prior to the PBS listing date through a patient support program. The PBAC considered it would be appropriate to enable access for grandfather patients who otherwise met the PBS criteria at the time of tucatinib initiation including the criteria around prior therapies.

7.19 The PBAC advised that tucatinib is not suitable for prescribing by nurse practitioners given the toxicity of the regimen.

7.20 The PBAC advised that tucatinib should be exempt from the Early Supply Rule given the maximum quantities are only sufficient for 21 days per supply at the maximum dose.

7.21 The PBAC advised that tucatinib should not be treated as interchangeable with any other drugs under Section 101 (3BA) of the *National Health Act 1953*.

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

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over trastuzumab plus capecitabine, particularly in patients with brain metastases, on the basis of the HER2CLIMB trial results;

b) The treatment is not expected to address a high and urgent unmet clinical need given other therapies are available;

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

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Initial treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
TUCATINIB					
tucatinib 150 mg tablet, 84	NEW	1	84	2	Tukysa
tucatinib 50 mg tablet, 88	NEW	1	88	1	Tukysa
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: Section 85 GENERAL – General Schedule (Code GE)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required – Streamlined [new code]					
Administrative Advice: Special pricing arrangements apply					
Administrative Advice: Authority applications for increased quantities/repeats (where relevant) may be made via the Online PBS Authorities system or by telephone to Services Australia on 1800 888 333					
Episodicity: [blank]					
Severity: Metastatic (Stage IV)					
Condition: HER2 positive breast cancer					
Indication: Metastatic (Stage IV) HER2 positive breast cancer					
Treatment Phase: Initial treatment					
Clinical criteria					
Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) either in the primary tumour or a metastatic lesion					
AND					
Clinical criteria:					
The condition must have progressed following treatment with at least two different HER2-directed regimens for metastatic breast cancer; OR					
The condition must have progressed following treatment with T-DXd for HER2+ metastatic breast cancer					
AND					
Clinical criteria:					
Patient must have a WHO performance status of 0 or 1 prior to initiating treatment with this drug					
AND					
Clinical criteria					
The treatment must be initiated in combination with trastuzumab and capecitabine					
Administrative Advice: HER2 gene amplification need not be re-confirmed. The evidence obtained from when the patient was treated with a prior HER2-directed regimen is sufficient.					
Prescribing Instructions: At the time of the authority application, the prescriber should request an appropriate quantity and number of repeats for the strength(s) required; according to the patients dosing schedule in the TGA approved Product Information.					

Continuing treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
TUCATINIB					
tucatinib 150 mg tablet, 84	NEW	1	84	2	Tukysa
tucatinib 50 mg tablet, 88	NEW	1	88	1	Tukysa
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: Schedule 85 GENERAL – General Schedule (Code GE)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required – Streamlined [new code]					
Administrative Advice Special pricing arrangements apply					
Administrative Advice: Authority applications for increased quantities/repeats (where relevant) may be made via the Online PBS Authorities system or by telephone to Services Australia on 1800 888 333					
Indication: Metastatic (Stage IV) HER2 positive breast cancer					
Treatment Phase: Continuing treatment					
Clinical criteria					
Patient must have previously received PBS-subsidised treatment with this drug for metastatic (Stage IV) HER2 positive breast cancer					
AND					
Clinical criteria:					
Patient must not have developed disease progression while receiving treatment with this drug for this condition.					
AND					
Treatment criteria:					
Patient must have initiated as a triple drug-regimen, following issuance of this prescription, consisting of: (i) tucatinib, (ii) capecitabine, (iii) trastuzumab					
Prescribing Instructions: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.					
Prescribing Instructions: The treatment must not exceed a lifetime total of one continuous course for this PBS indication.					
Prescribing Instructions: At the time of the authority application, the prescriber should request an appropriate quantity and number of repeats for the strength(s) required; according to the patients dosing schedule in the TGA approved Product Information.					

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

Pfizer Australia acknowledges the healthcare professionals, professional societies, patient organisations and consumers who supported the re-submission for TUKYSA® (tucatinib). Pfizer welcomes the PBAC's acknowledgement of the unmet need for patients in Australia living with HER2+ metastatic breast cancer and the positive recommendation. Pfizer is disappointed that the recommended price does not reflect the value of this innovative medicine and its expected use in Australian clinical practice. Unfortunately, this means that TUKYSA® will not be made available on the PBS.