5.17 TUCATINIB, Tablet 50 mg, Tablet 150 mg, TUKYSA®, Lucid Health Consulting Pty Ltd

1 Purpose of submission

1.1 The submission requested General Schedule Section 85 listing for tucatinib in combination with trastuzumab and capecitabine for the management of HER2-positive (HER2+) metastatic breast cancer (mBC), including patients with brain metastases. This is the first application to PBAC for the use of tucatinib.

1.2 Listing was requested on the basis of a cost-effectiveness analysis of tucatinib in combination with trastuzumab and capecitabine compared with placebo plus trastuzumab and capecitabine. The key components of the clinical issue presented in the submission are summarised in Table 1.

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

Component	Description
Population	Stage IV metastatic HER2+ breast cancer, including patients with brain metastases. The PSCR clarified that the intended population comprises patients who have progressed following: • ≥ 2 prior lines of HER2-directed therapy in metastatic disease (3rd or later-line mBC); or • 1 prior line of HER2-directed therapy for metastatic disease where the patient has previously received T-DM1 for either adjuvant or metastatic disease (2nd line mBC and adjuvant T-DM1).
Intervention	Tucatinib 300 mg twice daily Capecitabine 1000 mg/m^2 for days 1-14 only of a 21-day cycle Trastuzumab 8 mg/kg on the first day of the initial 21-day cycle, followed by 6 mg/kg on the first day of each subsequent 21-day cycle OR 600 mg subcut Day 1 every 21 days Treatment to continue until disease progression or intolerance.
Comparator	Capecitabine 1000 mg/m^2 for days 1-14 only of a 21-day cycle Trastuzumab 8 mg/kg on the first day of the initial 21-day cycle, followed by 6 mg/kg on the first day of each subsequent 21-day cycle OR 600 mg subcut Day 1 every 21 days Treatment to continue until disease progression or intolerance.
Outcomes	Primary endpoint: PFS on first 480 patients randomised; Secondary endpoints, assessed in the total population (612 patients),[a] included OS, PFS among patients with brain metastases, confirmed objective response rate, quality of life as measured by EQ-5D-5L questionnaire, and safety.
Clinical claim	In previously treated patients with HER2+ mBC, including those with brain metastases, tucatinib added to trastuzumab and capecitabine is superior in efficacy and inferior in safety, when compared with trastuzumab and capecitabine. The addition of tucatinib results in an inferior but manageable safety profile.

Source: Table 1.1 p20-1 of the submission.

HER2+ = human epidermal growth factor receptor 2 positive; ITT = intention to treat; IV = intravenous; mBC = metastatic breast cancer; OS = overall survival; PFS = progression free survival; PSCR = pre-Sub-Committee response; subcut = subcutaneously; T-DM1 = ado-trastuzumab emtansine

[a] The submission stated key secondary outcomes were assessed in all randomised patients but PFS among patients with brain metastases was a prespecified subgroup (48% of the ITT-OS population), confirmed objective response rate was undertaken in the subgroup of the ITT-OS population with measurable disease (87% of the ITT-OS population), and quality of life data collection was only undertaken in 54% of the ITT-OS population following a late protocol amendment.

2 Background

Registration status

2.1 Tucatinib was TGA registered on 13 August 2020 following a priority review, for the following indication: "TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting."

2.2 The TGA evaluation of this submission was completed as a 'Project Orbis' collaboration between the FDA, Health Canada, Swissmedic, HSA (Singapore) and TGA. A document that reflects this collaborative review (the "Multi-Discipline Review") is publicly available on the FDA website[1].

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

3 Requested listing

3.1 The restriction proposed in the submission is outlined below, with amendments proposed in the Pre-Sub-Committee Response (PSCR) in italics.

[1] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213411Orig1s000MultidisciplineR.pdf

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
TUCATINIB Tablets 150mg (84)	168	1 (initial) 0(continuing)	Published Price (SPA) AEMP per pack $[redacted] DPMQ $[redacted] Effective Price AEMP per pack $[redacted] DPMQ $[redacted]	TUKYSA	Seagen Inc.
Tablets 50mg (88)	176	1 (initial) 0(continuing)	Published Price (SPA) AEMP per pack $[redacted] Public DPMQ $[redacted] Effective Price AEMP per pack $[redacted] Public DPMQ $[redacted]	TUKYSA	Seagen Inc.

Source Table 1.8 p46 of the submission.

Category / Program	General schedule Section 85
Prescriber type:	☒Medical Practitioners
PBS Indication:	Metastatic (Stage IV) HER2 positive breast cancer
Treatment phase:	Initial
Restriction type:	☒Authority Required (immediate/real-time assessment by Services Australia)
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 The condition must have progressed following treatment with at least two prior HER2-directed *regimens* for metastatic breast cancer OR The condition must have progressed following treatment with one prior HER2-directed *regimen* for metastatic breast cancer in circumstance that T-DM1 *has been used in the adjuvant or metastatic setting* AND Patient must have a WHO performance status of 0 or 1 AND The treatment must be in combination with trastuzumab and capecitabine AND The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure.	
Prescriber Instructions Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval	
Administrative Advice	

Note Special Pricing Arrangements Apply Note Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001

Source: Table 1.10, p51 of the submission and pp 1-2 of the PSCR.

Category / Program	General schedule Section 85
Prescriber type:	☒Medical Practitioners
PBS Indication:	Metastatic (Stage IV) HER2 positive breast cancer
Treatment phase:	Continuing
Restriction type:	☒Authority Required - Streamlined
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for metastatic (Stage IV) HER2 positive breast cancer AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug, AND The treatment must be in combination with trastuzumab and capecitabine AND The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure.	
Prescriber 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.	
Administrative Advice Note Special Pricing Arrangements Apply Note Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001	

Source: Table 1.11, p52 of the submission.

3.2 The pre-PBAC response, noting that the cycle length of treatment with tucatinib, trastuzumab and capecitabine is 21 days, stated that the maximum quantities for both strengths of tucatinib should correspond to 21 days of therapy (i.e. the maximum

quantity should be 1 pack, rather than 2). The PBAC noted that PBS listings generally supply 28 or 30 days of therapy per dispensing.

3.3 In the key trial, HER2CLIMB, patients were required to have received prior trastuzumab, pertuzumab and T-DM1 (for the treatment of adjuvant, neoadjuvant or metastatic disease).

3.4 The PSCR stated that the requested listing is intended to allow use of tucatinib in patients with HER2+ mBC who have progressed following treatment with:

- at least two prior lines of HER2-directed therapy for metastatic disease (3rd or later-line mBC treatment); or
- one prior line of HER2-directed therapy for metastatic disease where the patient has previously been treated with trastuzumab emtansine (T-DM1) as either adjuvant treatment or for metastatic disease (2nd line treatment of mBC and adjuvant T-DM1treatment).

3.5 The second dot point and the proposed restriction are inconsistent with the clinical trial as they do not require patients to have received prior pertuzumab. For example patients would be eligible for tucatinib as second-line treatment for metastatic disease without prior pertuzumab if they received T-DM1 in the following circumstances:

- for first-line metastatic disease; or
- as adjuvant treatment followed by single agent trastuzumab as first-line treatment for metastatic disease.

The pre-PBAC response stated that patients most likely would have had prior pertuzumab neoadjuvant treatment either by the Special Access Program or self-funded. The PBAC considered that only patients at highest risk of relapse would be likely to self-fund pertuzumab, particularly given the availability of adjuvant T-DM1 (see paragraph 3.9).

3.6 The evaluation considered that specifying the required prior HER2-directed therapies would add clarity to the restriction. The PSCR stated that the therapies were not named as the treatment landscape may change over time, however the ESC considered that it may be reasonable to specify the required prior therapies (trastuzumab, pertuzumab and T-DM1) in this case.

3.7 The HER2CLIMB eligibility criteria did not specify the setting, in terms of use as adjuvant/neoadjuvant treatment, or, for metastatic/non metastatic disease, in which patients were required to have received prior trastuzumab, pertuzumab and T-DM1. While the majority of patients in the trial received these therapies for metastatic disease only (59.8%, 86.7%, and 98.8%, respectively, in the ITT-PFS population), some patients received these therapies for both metastatic disease and as neoadjuvant/adjuvant treatment (33.3%, 4.0%, and 0.2%, respectively), and some received them as neoadjuvant/adjuvant treatment only (6.9%, 9.2%, and 1.0%,

respectively). In practice, clinicians would be unlikely to re-treat patients with T-DM1 or pertuzumab for metastatic disease after receiving these agents as neoadjuvant or adjuvant treatment. However, the PBAC considered re-treatment with trastuzumab, particularly in combination with different chemotherapy or targeted therapies, upon relapse, is accepted clinical practice.

3.8 The proposed restriction allows use of tucatinib as second-line treatment for metastatic disease in patients who received T-DM1 adjuvant treatment. Although only 1% of patients in the HER2CLIMB study had received T-DM1 adjuvant treatment (and only 6% of patients in HER2CLIMB received second-line treatment for metastatic disease), this was because the study design pre-dated the release of results from the pivotal study of T-DM1 in this setting (the KATHERINE study). Adjuvant T-DM1 use was TGA-approved in 2019 and PBS-listed in April 2020, and is now standard of care for those patients who do not achieve a pathological complete response following neoadjuvant therapy that included trastuzumab and taxane-based chemotherapy.

3.9 The requested restriction does not account for use of neoadjuvant pertuzumab. Neoadjuvant pertuzumab is not PBS-listed and the proportion of patients who self-fund pertuzumab was unclear, but was estimated (by the sponsor of pertuzumab) to be 20% prior to the PBS listing of T-DM1 (paragraph 6.49, T-DM1 Public Summary Document (PSD), November 2019). While neoadjuvant pertuzumab is more likely to be recommended to patients at the greatest risk of developing metastatic disease, the availability of adjuvant T-DM1 may influence and lower uptake.

3.10 Specifically, the proposed restriction does not allow use of tucatinib as second-line treatment for metastatic disease in patients who relapse following a neoadjuvant pertuzumab + trastuzumab based regimen (noting these patients would meet the HER2CLIMB eligibility criteria with just T-DM1 for metastatic disease). About 6% of patients who enrolled in HER2CLIMB received tucatinib as second-line treatment for metastatic disease, comprising predominantly of those who received neoadjuvant pertuzumab. The PSCR stated that the sponsor is amenable to allowing tucatinib to be used in this situation. The ESC considered that it would be reasonable to allow patients who relapse following self-funded neoadjuvant pertuzumab to access tucatinib as second-line treatment for metastatic disease.

3.11 The evaluation also noted that the proposed restriction does not allow use of tucatinib as first-line treatment of metastatic disease in patients who experienced disease progression following neoadjuvant pertuzumab and adjuvant T-DM1 (i.e. prior to the detection of metastatic disease). Such use would be outside the TGA indication and inconsistent with HER2CLIMB in which all patients received at least one line of therapy for metastatic disease. The PSCR clarified that listing was not sought for first-line treatment of metastatic disease.

3.12 There is a risk of leakage of tucatinib to an earlier line of therapy in patients with brain metastases not amenable to treatment with, or who are seeking to delay/avoid, other

interventions such as surgery or radiation therapy and other systemic therapies which have limited efficacy.

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 with a propensity for early relapse following adjuvant therapy. Visceral metastases (and in particular, liver metastases) are more common in those with HER2+ mBC than other breast cancer subtypes, and up to 50% of patients with HER2+ mBC develop brain metastases at some point in the course of their disease. HER2+ breast cancer accounts for approximately 15-20% of all new breast cancer diagnoses. There is significant unmet need for an effective systemic therapy that treats brain metastases, as most approved regimens have very limited efficacy.

4.2 The proposed population is made up of two groups:

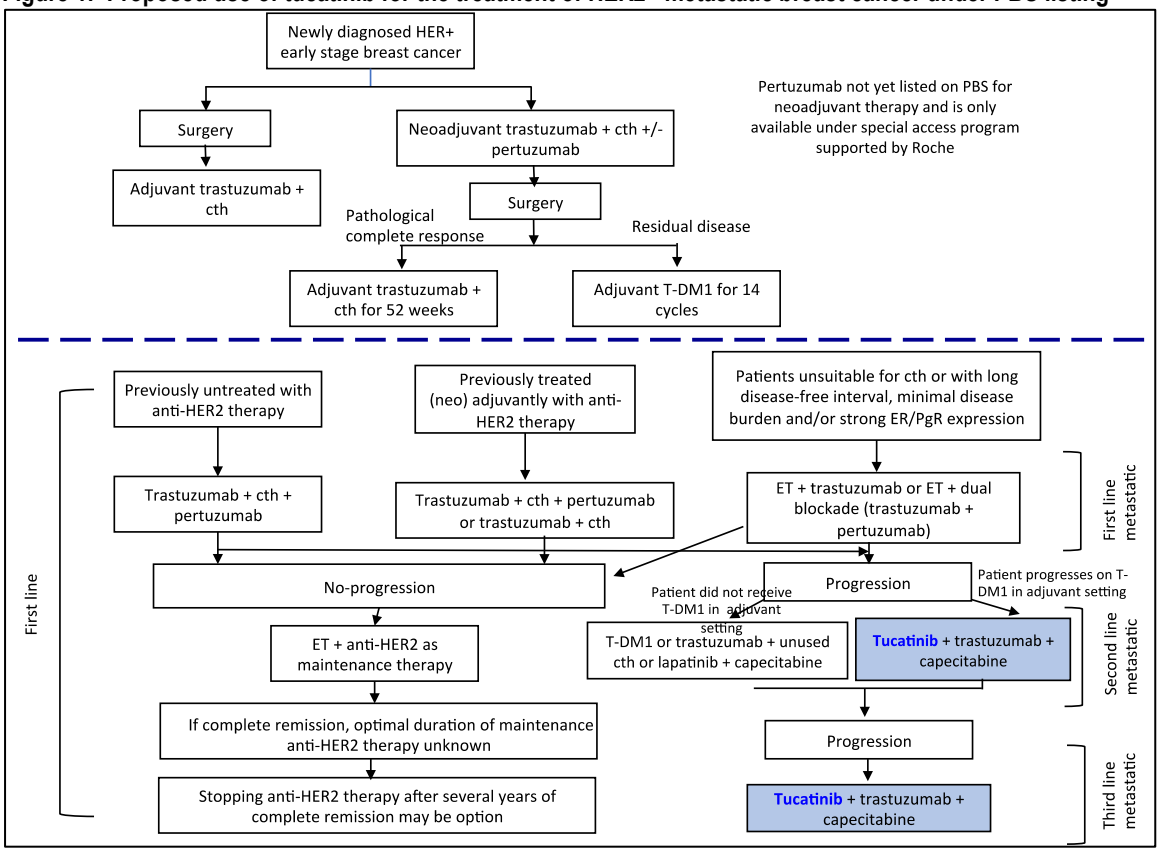
- those with relapse following diagnosis of their breast cancer at an earlier stage of disease who would usually have received adjuvant treatment, and
- those presenting with metastatic disease at the time of their initial diagnosis (known as '*de novo*' metastatic disease) who have not received any prior systemic therapies.

4.3 Patients in the first group will almost always have received adjuvant therapy with curative intent - either a trastuzumab-based regimen as (neo)adjuvant therapy or a combination of neoadjuvant trastuzumab with a switch to postoperative T-DM1 for completion, and a small proportion may have elected to self-fund pertuzumab or accessed other experimental HER2-directed therapies in early disease. Of those relapsing after adjuvant therapy with T-DM1, approximately up to 6% will present with CNS recurrence as their first site of relapse (von Minckwitz et al, 2019)[2].

4.4 Those presenting with metastatic disease at the time of their initial diagnosis have received no prior treatment and have a higher likelihood of developing brain metastases earlier in the course of their disease. Despite this, their response rate to therapies is likely to be higher and their prognosis is better than those with the same disease burden who have received systemic treatment for early breast cancer.

[2] von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;380:617-28.
https://www.nejm.org/doi/suppl/10.1056/NEJMoa1814017/suppl_file/nejmoa1814017_appendix.pdf

Figure 1: Proposed use of tucatinib for the treatment of HER2+ metastatic breast cancer under PBS listing



Source Figure 1.6, p43 of the submission.
cth = chemotherapy; ET = endocrine therapy (estrogen receptor and progesterone receptor); HER2+ = human epidermal growth factor receptor 2 positive; T-DM1 = ado-trastuzumab emtansine

4.5 The clinical algorithm (Figure 1, above) would appear to allow patients to receive tucatinib for third-line metastatic disease without prior pertuzumab or T-DM1. For example, for first-line metastatic disease, the algorithm allows use of endocrine therapy + trastuzumab or endocrine therapy + dual blockage (trastuzumab + pertuzumab), and as such does not require patients to have received prior pertuzumab. This is not consistent with the proposed restriction or the clinical evidence presented, with the latter requiring patients to have received prior pertuzumab, trastuzumab and T-DM1 (for the treatment of adjuvant, neoadjuvant or metastatic disease).

4.6 Tucatinib is a tyrosine kinase inhibitor of HER2.

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

5 Comparator

5.1 As tucatinib is an add-on to the established regimen of trastuzumab plus capecitabine, the submission nominated trastuzumab plus capecitabine as the comparator.

5.2 There is no third-line standard of care following progression on a pertuzumab-based regimen and T-DM1, but continuation of an anti-HER2 agent is standard. The PBS data support that patients in Australia are likely to receive a continuation of trastuzumab in combination with chemotherapy that has not been used previously, such as capecitabine. Although PBS-listed in this setting, lapatinib plus capecitabine has substantial toxicity and limited efficacy, and PBS data indicates it is not used widely in Australia. Alternative options also include enrolment in a clinical trial.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with tucatinib in terms of treating brain metastases.

6.3 The PBAC noted the advice received from the Breast Cancer Network Australia clarifying the likely use of tucatinib in clinical practice. The PBAC specifically noted the advice that the use of tucatinib may lower the risk of progression for patients with brain metastases and increase survival and improve quality of life for patients with HER2+ breast cancer. The PBAC noted that this advice was supportive of the evidence provided in the submission.

The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the tucatinib submission, categorising it as one of the therapies of "high 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 in combination with trastuzumab and capecitabine, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[1], based on a comparison with placebo in combination with trastuzuamb and capecitabine[3].

Clinical trials

6.4 The submission was based on one randomised, multinational, controlled, double-blind Phase II study, comparing treatment with tucatinib in combination with trastuzumab and capecitabine versus placebo plus trastuzumab and capecitabine. The trial was

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

conducted in patients with metastatic HER2+ breast cancer who had received prior therapy for the treatment of metastatic disease.

6.5 Details of the study presented in the submission are provided in the table below.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
HER2CLIMB (NCT02614794) A Phase 2 Randomised, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma	Clinical Study Report	7 Nov 2019
	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, 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.	Annals of Oncology. Conference: ESMO Breast Cancer Virtual Meeting 2020. Switzerland. 31 (Supplement 4) (pp S348-S395), 2020.
	Curigliano G, Murthy R, Loi S, et al. Tucatinib vs placebo added to trastuzumab and capecitabine in previously treated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB).	Annals of Oncology. Conference: ESMO Breast Cancer Virtual Meeting 2020. Switzerland. 31 (Supplement 2) (pp S62-S63), 2020.

Source: Table 2.2, pp58-59 of the submission.

6.6 The key features of the randomised trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Tucatinib, trastuzumab, capecitabine placebo, trastuzumab, capecitabine						
HER2CLIMB	612	R, DB, MC, PC Ongoing Median follow-up 26 months	Low except for HRQoL	HER2+ mBC, progressed after at least one HER2-directed therapy	Primary: PFS Secondary: OS, ORR, $PFS_{Brainmets}$	PFS, OS, HR-QoL, safety and tolerability

Source: Text and Table 2.22, pp88-9 of the submission}.
DB = double blind; HER2+ = human epidermal growth factor receptor 2 positive; HRQoL = health related quality of life; mBC = metastatic breast cancer; MC = multi-centre; ORR = objective response rates; OS = overall survival; PC = placebo-controlled; PFS = progression-free survival; R = randomised;

6.7 The risk of bias was low apart from the approach to collection of the health-related quality of life (HRQoL) data, which only commenced after more than 40% of patients had enrolled. The EQ-5D-5L was the sole HRQoL instrument used, but it is not designed to capture the impact of treatment, especially toxicities that were likely to be encountered. The pre-PBAC response stated that the impact of treatment-related toxicities was likely to be low. Baseline questionnaires were completed by 54% of study participants, and last visit data collection was available for 20% of participants (i.e. as a proportion of the total study population, the ITT-OS population). Given the substantial missing data, the evaluation and the ESC considered that no conclusions can be drawn about the impact of treatment on HRQoL.

6.8 Patients with brain metastases were permitted to enrol in HER2CLIMB, including those with treated and previously untreated brain metastases. Such patients are usually excluded from clinical trials, due to their poor prognosis and because most agents have limited efficacy against brain metastases. However, such patients were deliberately included based on efficacy signals early in the tucatinib development program, and an analysis of their PFS outcomes as an alpha-controlled subgroup analysis was a key secondary outcome. Patients with brain metastases comprised 48% of the ITT-OS population.

6.9 The sample size was increased from 480 to 600 under protocol version 8 to increase the statistical power for analyses of key secondary endpoints, but the primary analysis of PFS by blinded independent central review (BICR) was kept to the first 480 patients to reduce potential bias due to early progression events and shorter follow-up in patients recruited later. This approach resulted in different analysis populations for the primary endpoint and those used for the secondary endpoints.

- The ITT-OS analysis population included all randomised patients. The analyses of the key secondary endpoints OS and confirmed ORR per BICR were conducted on all randomised patients in the ITT-OS population.
- The analysis for the primary endpoint of PFS per BICR was conducted using the first 480 randomised patients in the ITT-OS analysis population (ITT-PFS population).
- The analyses of the key secondary endpoint $PFS_{BrainMets}$ were conducted in all randomised patients with brain metastases in the ITT-OS population (ITT-$PFS_{BrainMets}$ population). This was the only subgroup analysis for which an alpha was allocated.

6.10 All pre-specified subgroup analyses for the primary endpoint and key secondary efficacy endpoints (subgroup analyses on the ITT-PFS, ITT-OS and ITT-$PFS_{BrainMets}$ populations), based on demographics and disease characteristics, were exploratory as no alpha was allocated.

6.11 In HER2CLIMB, patients enrolled were heavily pre-treated and had received a median of 4 prior lines of systemic therapy (range: 1-14) and a median of 3 prior lines of treatment for metastatic disease. In HER2CLIMB, only 6% of patients received tucatinib as a second-line metastatic treatment. Use in this setting will likely be higher in the proposed PBS population due to use of T-DM1 for the treatment of adjuvant disease (which was not standard practice at the time HER2CLIMB was conducted). The submission stated that the Cox-regression analyses indicated a consistency of treatment effect irrespective of the number of prior lines of metastatic therapy and the test for interaction was non-significant (p = 0.436). This was an exploratory analysis, based on small patient numbers. Overall patients in HER2CLIMB may be more heavily pre-treated than those in Australian clinical practice, and it is unclear whether this will impact the absolute benefit of tucatinib.

Comparative effectiveness

6.12 The primary efficacy and key secondary efficacy outcomes are outlined in the table below.

Table 4: Summary of primary efficacy and key secondary efficacy outcomes in HER2CLIMB

	Tucatinib + trastuzumab + capecitabine	Placebo + trastuzumab + capecitabine	Absolute difference	HR (95% CI)
Progression-free survival (ITT-PFS population = first 480 patients randomised)				
N	320	160		
Progressed, n/N (%)	178 (56%)	97 (61%)	-	-
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-value<0.000012**
% 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)				
N	410	202		
Deaths, n (%)	130 (31.7%)	85 (42.1%)	-	-
Median OS, months (95% CI)	**21.9 (18.3, 31.0)**	**17.4 (13.6, 19.9)**	**4.5 months**	**0.66 (0.50, 0.88) p-value<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)				
N	198	93		
Progressed, n (%)	106/198 (53.5%)	51/93 (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-value<0.00001**
Confirmed ORR per BICR (Patients with measurable disease, subgroup of ITT-OS)				
N	340	171		
ORR n/N (%)	**138/340 (40.6%)**	**39/171 (22.8%)**	**17.8%**	**p-value<0.00008[1]**
(95% CI)	(35.3%, 46.0%)	(16.7%, 29.8%)	-	-
CR (%)	3 (0.9%)	2 (1.2%)	-	-
PR (%)	135 (39.7%)	37 (21.6%)	-	-
Duration of response (not key secondary efficacy endpoint) (Patients with response, subgroup of ITT-OS population)				
Median, months (95% CI)	8.3 (6.2, 9.7)	6.3	2 months	-

Source: pp95-105 of the submission (corrected figures in italics per Table 17, p82 of CSR) and FDA label accessible at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213411s000lbl.pdf

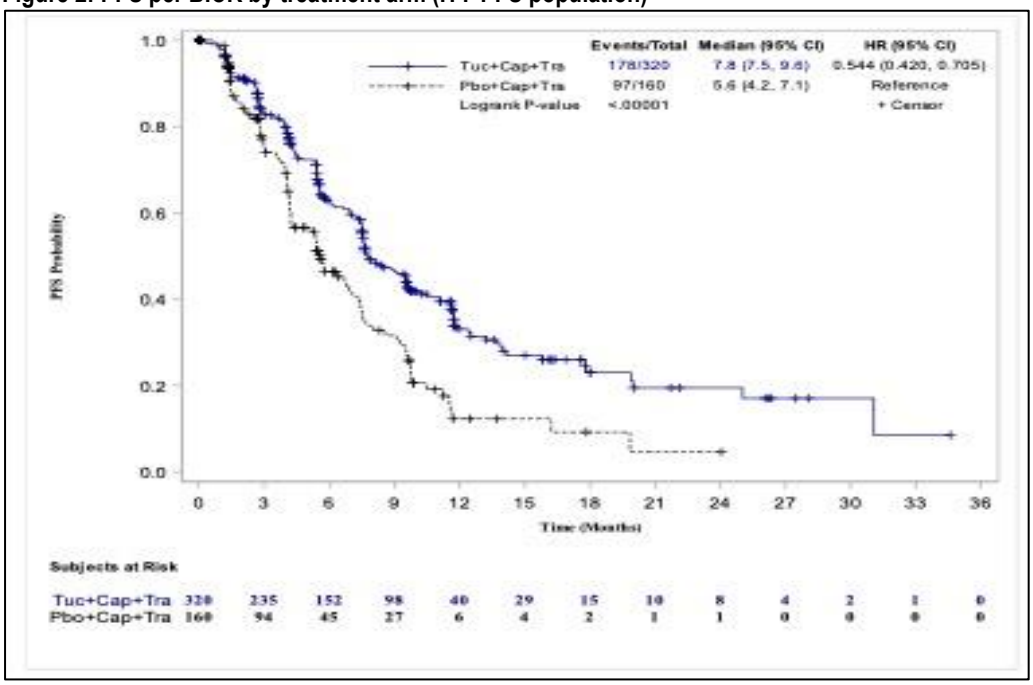
BICR = blinded independent central review; CI = confidence interval; CR = complete response; HR = hazard ratio; ITT = intention to treat; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response

[1]Stratified CMH p-value for ORR.

Primary efficacy endpoint – PFS per blinded independent central review (BICR)

6.13 After a median follow-up of 10.4 months, the addition of tucatinib to trastuzumab and capecitabine was associated with a 46% reduction in the risk of progression or death (HR = 0.54; 95% CI: 0.42, 0.71; p<0.00001) and a median improvement in PFS of 2.2 months compared with placebo plus trastuzumab and capecitabine (Figure 2).

Figure 2: PFS per BICR by treatment arm (ITT-PFS population)



Source: Figure 3, p79 of HER2CLIMB CSR
BICR = blinded independent central review; Cap = capecitabine; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; Pbo = placebo; PFS = progression free survival; Tra = trastuzumab; Tuc = tucatinib

6.14 The results of subgroup analyses were consistent with the primary efficacy outcome. Sensitivity analyses of PFS per investigator were also consistent, with a greater degree of concordance between BICR and investigators when initiation of a new therapy was also listed as a PFS event (analysis requested by the FDA)[4]. Sensitivity analyses of PFS in the larger ITT-OS population were also consistent.

Secondary efficacy endpoints

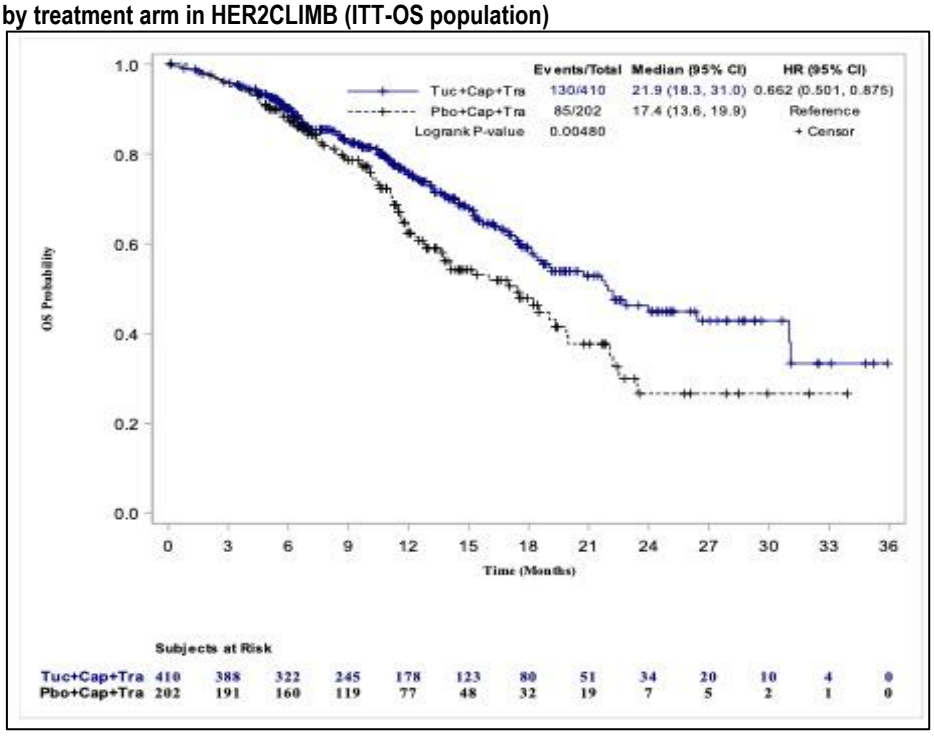
Secondary efficacy endpoint – overall survival

6.15 After a median follow-up time of 14 months and following 60% of the planned OS events, median overall survival (OS) was prolonged by 4.5 months (21.9 months (95% CI: 18.3, 31.0) versus 17.4 months (95% CI: 13.6, 19.9)) in the tucatinib arm versus the

[4] p137 FDA Multidisciplinary Review
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213411Orig1s000MultidisciplineR.pdf

placebo arm, respectively. There was a statistically significant 34% reduction in the risk of death (HR = 0.66; 95% CI: 0.50, 0.88; p = 0.0048) (Figure 3).

Figure 3: OS by treatment arm in HER2CLIMB (ITT-OS population)



Source: Figure 5, p83 of HER2CLIMB CSR
Cap = capecitabine; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; OS = overall survival; Pbo = placebo; Tra = trastuzumab; Tuc = tucatinib

6.16 Subgroup analyses indicated a consistent treatment effect across the subpopulations analysed, although these were exploratory only.

<u>Secondary efficacy endpoint – PFS in patients with brain metastases per BICR</u>

6.17 In patients with brain metastases (ITT-$PFS_{BrainMets}$), the addition of tucatinib resulted in a statistically significant 52% reduction in the risk of disease progression (in the brain or elsewhere) or death in patients with brain metastases (stratified HR= 0.48; 95% CI: 0.34, 0.69; p < 0.00001). The median PFS was 7.6 months (95% CI: 6.2, 9.5) in the tucatinib arm versus 5.4 months (95% CI: 4.1, 5.7) in the control arm.

6.18 Estimated PFS in this population at 12 months was 25% (95% CI: 16.5%, 34.3%), compared with 0% in the comparator arm.

Additional analyses in patients with brain metastases

6.19 While not a prespecified analysis and therefore exploratory (with a nominal p value), the submission presented an additional analysis of OS in patients with brain metastases. There was a reduced risk of death by 42% (HR = 0.58; 95% CI: 0.40, 0.85; p = 0.005) in patients with brain metastases.

6.20 Lin et al (2020) provided additional exploratory analyses of outcomes in the HER2CLIMB ITT-$PFS_{BrainMets}$ population: with the addition of tucatinib, response rates in brain lesions were increased by 27%, and the median intracranial PFS as judged by progression in brain metastases or death among those with brain lesions was increased by 5.7 months and median overall survival was improved by 6.1 months, which are presented in the table below. Further exploratory subgroup analyses (Bachelot et al, 2020[5] presented in an abstract form only) indicated that the treatment effect appears to be maintained regardless of whether the brain metastases were previously treated or untreated, stable or progressing.

Table 5: Summary of exploratory efficacy analyses in patients with brain metastases in HER2CLIMB (patients with brain metastases in ITT-OS population)

	Tuc + Cap + Tra (N = 198)	**Pbo + Cap + Tra (N = 93)**
Median CNS-PFS		
Median CNS-PFS (months) (95% CI)	9.9	4.2
Hazard ratio (95% CI) (p-value)	0.32 (0.22, 0.48) (< 0.0001)	
Median overall survival		
Median OS (months) (95% CI)	18.1	12.0
Hazard ratio (95% CI) (p-value)	0.58 (0.40, 0.85) (0.005)	
Intracranial overall response		
Response rate (95% CI)	47.3% (33.7%, 61.2%)	20.0% (5.7%, 43.7%)
Response duration (months) (95% CI)	6.8 (5.5, 16.4)	3.0 (3.0, 10.3)

Source: Lin et al., 2020[6] amended to have p values in italics, as these analyses are exploratory only.
Cap = capecitabine; CI = confidence interval; CNS = central nervous system; ITT = intent to treat; OS = overall survival; PFS = progression free survival; Pbo = placebo; Tra = trastuzumab; Tuc = tucatinib

6.21 While the study was not powered or designed to assess these outcomes, and the p value should be regarded as nominal, the response rates in particular support that tucatinib has a treatment effect on brain metastases.

[5] T. Bachelot *et al.* Impact of tucatinib on progression free survival in patients with HER2+ metastatic breast cancer and stable or active brain metastases. *Annals of Oncology* **31 (suppl_4):**, doi:10.1016/annonc/annonc268 (2020).

[6] Lin, N. U. *et al.* Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. *Journal of Clinical Oncology* 2020: **38**, 2610-2619

Secondary efficacy outcome – Objective response rate

6.22 The addition of tucatinib increased the ORR per BICR by 18% in patients with measurable disease: 40.6% (95% CI: 35.3%, 46.0%) versus 22.8% (95% CI: 16.7%, 29.8%) for the tucatinib and placebo arms, respectively. Complete responses were uncommon, and occurred in 3 patients in the tucatinib arm and 2 patients in the comparator arm.

Comparative harms

6.23 Key adverse events in the HER2CLIMB study are summarised in the table below. The median duration of treatment was longer in the tucatinib arm (5.8 months versus 4.4 months). There is considerable overlap between the toxicity profiles of tucatinib and capecitabine so the nature of the adverse events was similar in the two arms, with higher rates reported in the tucatinib arm, consistent with this being an add-on therapy.

Table 6: Summary of key adverse events in the HER2CLIMB trial

HER2CLIMB	Tucatinib + trastuzumab + capecitabine N = 404 n with event (n/N%)	Placebo + trastuzumab + capecitabine N = 197 n with event (n/N%)	RD (95% CI)
Any TEAE	401 (99.3%)	191 (97.0%)	0.023 (0.002, 0.044)
≥ Grade 3 TEAE	223 (55.2%)	96 (48.7%)	0.065 (-0.020, 0.150)
Any SAE	104 (25.7%)	53 (26.9%)	-0.012 (-0.086, 0.063)
TEAE leading to death	8 (2.0%)	6 (3.0%)	-0.011 (-0.036, 0.015)
Patients who discontinued any study treatment due to TEAE	45 (11.1%)	19 (9.6%)	0.015 (-0.038, 0.067)
Patients who discontinued tucatinib or placebo due to TEAE	23 (5.7%)	6 (3.0%)	0.026 (-0.010, 0.063)
Patients who discontinued capecitabine due to TEAE	41 (10.1%)	18 (9.1%)	0.010 (-0.041, 0.061)
Patients who discontinued trastuzumab due to TEAE	18 (4.5%)	5 (2.5%)	0.019 (-0.014, 0.052)

Source: Table 2.36, p112 of the submission.
CI = confidence interval; RD = risk difference; SAE = serious adverse event; TEAE = treatment emergent adverse event;

6.24 Treatment-emergent adverse events of any grade were common in both arms, but the following were more common in the tucatinib arm compared with the control arm: diarrhoea (80.9% vs. 53.3%), palmar-plantar erythrodysesthesia (PPE) syndrome (63.4% vs. 52.8%), nausea (58.4% vs. 43.7%), fatigue (45.0% vs. 43.1%), and vomiting (35.9% vs. 25.4%).

6.25 Adverse events that were determined by the sponsor to be associated with tucatinib included diarrhoea, elevated liver function tests (LFTs), nausea and vomiting, and stomatitis.

6.26 When adjusted for exposure using at-risk time, the incidence rate per 100 person-years of PPE syndrome was 21 and 19 on the tucatinib and control arms, respectively. This is considered to be related to capecitabine.

6.27 Severe adverse events (Grade ≥ 3 adverse reactions) occurred in more patients in the tucatinib arm than the control arm (Table 7). Those occurring at a frequency of ≥ 5% were: PPE syndrome (13% vs 9%), diarrhoea (13% vs 9%), nausea (4% vs 3%), hepatotoxicity by collated preferred terms per FDA Multidisciplinary review[7] (9% vs 3.6%), increased ALT, and fatigue by collated terms per FDA Multidisciplinary Review[7] (5% vs 4.5%).

Table 7: Grade ≥ 3 TEAEs in ≥ 2% of patients in the tucatinib arm in HER2CLIMB (Safety analysis population)

Preferred term	Tuc + Cap + Tra (N = 404) n (%)	Pbo + Cap + Tra (N = 197) n (%)
Patients with any event	223 (55.2%)	96 (48.7%)
Palmar-plantar erythrodysesthesia syndrome	53 (13.1%)	18 (9.1%)
Diarrhoea	52 (12.9%)	17 (8.6%)
Alanine aminotransferase increased	22 (5.4%)	1 (0.5%)
Fatigue	19 (4.7%)	8 (4.1%)
Aspartate aminotransferase increase	18 (4.5%)	1 (0.5%)
Anaemia	15 (3.7%)	5 (2.5%)
Nausea	15 (3.7%)	6 (3.0%)
Hypokalaemia	13 (3.2%)	10 (5.1%)
Pulmonary embolism	13 (3.2%)	4 (2.0%)
Vomiting	12 (3.0%)	7 (3.6%)
Hypophosphatemia	11 (2.7%)	4 (2.0%)
Stomatitis	10 (2.5%)	1 (0.5%)
Neutropenia	9 (2.2%)	9 (4.6%)

Source: Table 2.40, p115 of the submission.
Cap = capecitabine; Pbo = placebo; TEAE = treatment emergent adverse event; Tra = trastuzumab; Tuc = tucatinib

6.28 Withholding doses of tucatinib or placebo was more often required in the tucatinib arm compared with the control arm (54% vs 41%, respectively) and dose reductions were more common (21% vs 11%, respectively), mostly due to diarrhoea and LFT abnormalities. Most patients were able to resume at the same dose of tucatinib, or required a single dose reduction. Re-escalation of tucatinib following a dose reduction was not permitted per protocol. Dose reductions for capecitabine in both arms were more common than reductions in tucatinib. Discontinuation of therapy occurred in 5.7% of patients in the tucatinib arm, and 3% of the control arm while antidiarrhoeal treatments were required in 66% vs 36%, respectively. These indicate that with close

[7] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213411Orig1s000MultidisciplineR.pdf

monitoring, early intervention and supportive therapies that these adverse events are likely to be manageable in the majority of patients.

Benefits/harms

6.29 On the basis of the direct evidence presented by the submission, the comparison of tucatinib plus trastuzumab and capecitabine rather than placebo plus trastuzumab and capecitabine, resulted in:

- Approximately 21 additional patients alive without disease progression at one year (based on a median follow-up of 10.4 months);
- Approximately 13 additional patients alive at one year (based on a median follow-up of 14 months)

6.30 On the basis of direct comparison evidence presented by the submission, for every 100 patients treated with tucatinib plus trastuzumab and capecitabine in comparison with placebo plus trastuzumab and capecitabine with a median duration of exposure of 5.8 months in the tucatinib arm and 4.4 months in the comparator arm:

- Approximately 6 additional patients experienced a severe adverse event (≥ Grade 3) of any kind.
- Approximately 5 additional patients developed severe changes in liver function, but with dose reductions in the treatments, the proportions of patients stopping treatments were low in both arms (approximately 1 in 100 patients). Changes in liver function were common with both treatments, requiring regular blood tests.
- Approximately 27 additional patients experienced diarrhoea of any grade, with 4 additional patients (per 100 patients) experiencing severe diarrhoea; an additional 30 patients required anti-diarrhoea medications; only 1 in 200 additional patients were reported to have stopped treatment altogether because of the diarrhoea.

Clinical claim

6.31 The submission described the combination of tucatinib plus trastuzumab and capecitabine as superior in terms of effectiveness compared with trastuzumab and capecitabine. This claim was adequately supported.

6.32 Data from the HER2CLIMB trial support the claim that the addition of tucatinib to trastuzumab and capecitabine improves PFS and OS in patients with metastatic HER2+ breast cancer 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.

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

6.34 Due to the limitations in the quality of life data, no conclusions could be drawn about the impact of treatment on quality of life or symptom control.

6.35 The submission described the combination of tucatinib plus trastuzumab and capecitabine as inferior in terms of safety compared with trastuzumab plus capecitabine. This claim was appropriate, as this add-on therapy led to higher rates of adverse events, particularly diarrhoea and hepatotoxicity. The adverse events were largely manageable with close monitoring and early intervention.

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

Economic analysis

6.37 The submission presented a cost-utility analysis comparing tucatinib + capecitabine + trastuzumab with placebo + capecitabine + trastuzumab (abbreviated to tucatinib versus placebo), based on the HER2CLIMB trial. The key components of the economic evaluation are summarised in Table 8.

Table 8: Summary of model structure, key inputs and rationale

<table>
<tr><th>Component</th><th>Summary</th></tr>
<tr><td>Treatments</td><td>Tucatinib + capecitabine + trastuzumab versus placebo + capecitabine + trastuzumab (abbreviated herein to tucatinib versus placebo)</td></tr>
<tr><td>Time horizon</td><td>10 years in the model base case versus 10.4 months and 14 months median follow-up for PFS and OS, respectively, in the HER2CLIMB trial.</td></tr>
<tr><td>Outcomes</td><td>Life years gained, quality-adjusted life years</td></tr>
<tr><td>Methods used to generate results</td><td>Partitioned survival analysis</td></tr>
<tr><td>Health states</td><td>Progression-free, progressed disease, dead</td></tr>
<tr><td>Cycle length</td><td>1 week</td></tr>
<tr><td>Allocation to health states</td><td>Health state allocation determined by PFS and OS curves from HER2CLIMB followed by parametric extrapolations.
Kaplan-Meier curves were used until only very few patients remained at risk.</td></tr>
<tr><td>Extrapolation method</td><td>PFS: Log-logistic based on lowest AIC/BIC score
OS: Weibull based on lowest AIC/BIC score
Time to treatment discontinuation: Gompertz for the tucatinib arm based on visual inspection, however log-logistic was associated with a lower AIC/BIC score. No extrapolation was applied in the placebo arm (for the capecitabine + trastuzumab use).
Proportion hazards was assumed for PFS and OS.</td></tr>
<tr><td>Health related quality of life</td><td>Derived from HER2CLIMB EQ-5D-5L data. Different utilities were applied in each treatment arm and in different cycles as outlined below:
<table>
<tr><th></th><th>Tucatinib</th><th>Placebo</th></tr>
<tr><td colspan="3">Base case (based on HER2CLIMB EQ-5D-5L data)</td></tr>
<tr><td>Progression-free, cycles 1-2</td><td>0.823</td><td>0.845</td></tr>
<tr><td>Progression-free, cycles 3-4</td><td>0.835</td><td>0.835</td></tr>
<tr><td>Progression-free, cycles 5-6</td><td>0.859</td><td>0.808</td></tr>
<tr><td>Progression-free, cycles 7+</td><td>0.872</td><td>0.810</td></tr>
<tr><td>Progressed</td><td>0.738</td><td>Submission stated: 0.778
Actually applied: 0.738</td></tr>
<tr><td colspan="3">Sensitivity analysis: Lloyd et al, 2006</td></tr>
<tr><td>Progression-free</td><td colspan="2">0.786</td></tr>
<tr><td>Progressed</td><td colspan="2">0.538</td></tr>
</table>
The utility values applied in the base case were unreliable and appeared overly high.</td></tr>
</table>

Source: Compiled during evaluation.

AIC = Akaike information criteria; BIC = Bayesian information criteria; OS = overall survival; PFS = progression free survival;

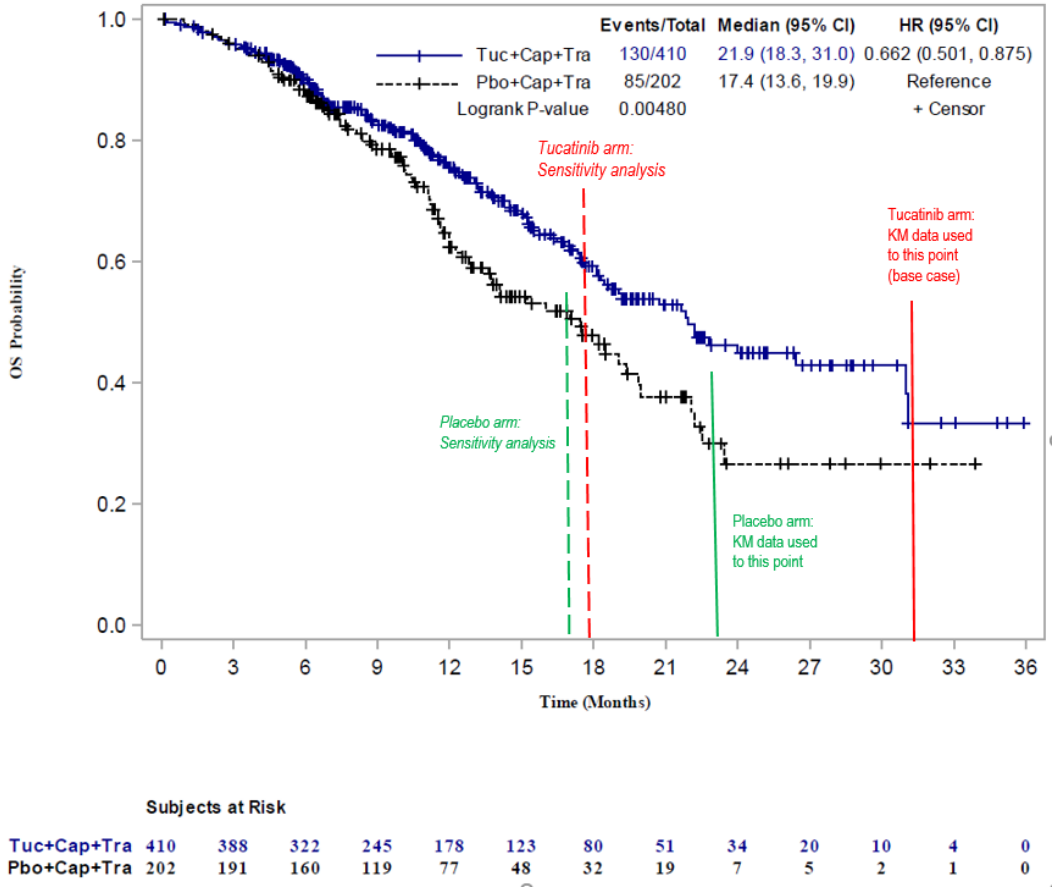
6.38 The submission used a partitioned survival approach with three health states (progression-free, progressed disease and death). Survival curves from HER2CLIMB were extrapolated using parametric survival models fitted to the individual patient data from the September 2019 data-cut (using the ITT-PFS population for PFS and the ITT-OS population for OS).

6.39 For PFS and OS, the submission assumed that the proportional hazard assumption was met, and applied joint statistical models containing a single covariate representing the treatment arm.

6.40 The model used Kaplan-Meier data until a time-point at which very few patients remained at risk. For PFS, Kaplan-Meier data were used until fewer than two patients remained at risk; for OS, as shown in the figure below, Kaplan-Meier data were used until fewer than ten patients remained at risk in the tucatinib arm. The submission did not provide any justification as to why these time-points were chosen. The 'Guidelines for Preparing a Submission to the PBAC' (version 5.0, September 2016) state: "where extrapolation is undertaken, use observed time-to-event data in preference to modelled data up to the time point at which the observed data become unreliable as a result of small numbers of patients remaining event-free". Given the very low number of patients still at risk at these time-points, the Kaplan-Meier estimates are unlikely to be reliable at these time-points.

6.41 The PSCR included a sensitivity analysis in which only the extrapolated curves were used (i.e. no Kaplan-Meier data were applied in the model). However, this does not align with the PBAC guidelines which, as noted in the paragraph above, state that observed time-to-event data should be used in preference to modelled data up to the time point at which the observed data become unreliable.

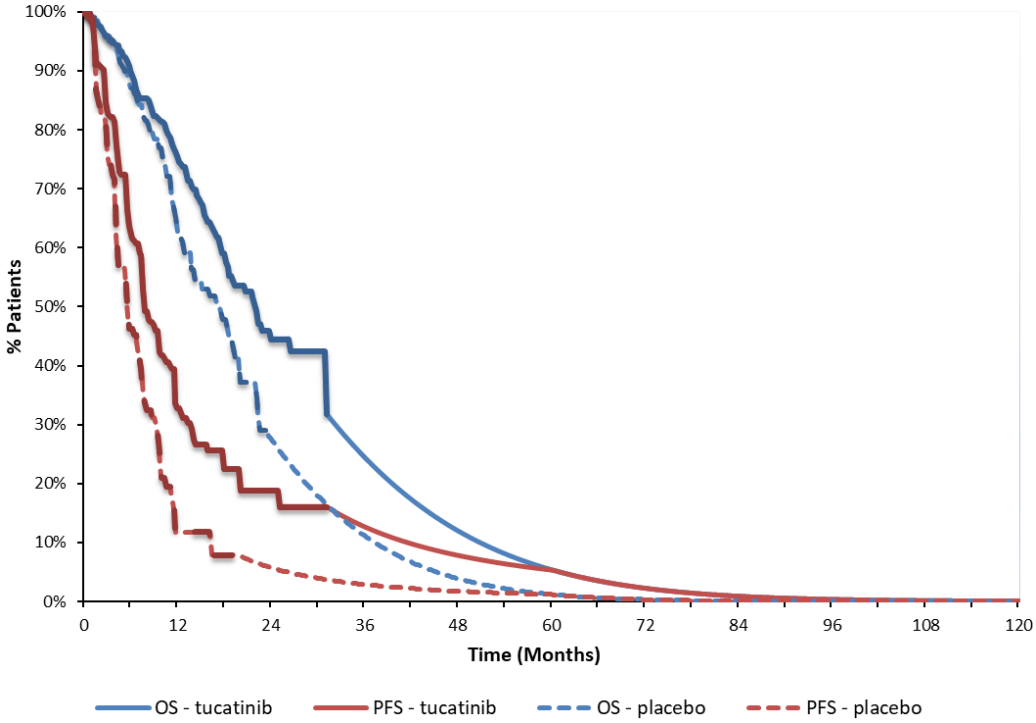
Figure 4: OS by treatment arm (ITT-OS population); red and green lines indicate the point up until which Kaplan-Meier data were used in the tucatinib and placebo arms, respectively (base case of model); dotted lines indicate the point up until which Kaplan-Meier data were used in sensitivity analyses conducted during evaluation (i.e. when 20% of patients remain at risk)



Source: Figure 5, p83 of HER2CLIMB CSR76
Cap = capecitabine; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; OS = overall survival; Pbo = placebo; Tra = trastuzumab; Tuc = tucatinib

6.42 The figure below shows the PFS and OS data applied in the model (which uses the Weibull model). The darker shades indicate use of Kaplan-Meier data, while lighter shades indicate use of extrapolated data.

Figure 5: PFS and OS data applied in the model (base case, Weibull model)



Source: 'Attachment 08 - Tucatinib mBC CEM_Final.xlsx', worksheet 'PSM Trace'; Darker lines indicate Kaplan-Meier data; lighter lines indicate extrapolations
OS = overall survival; PFS = progression free survival

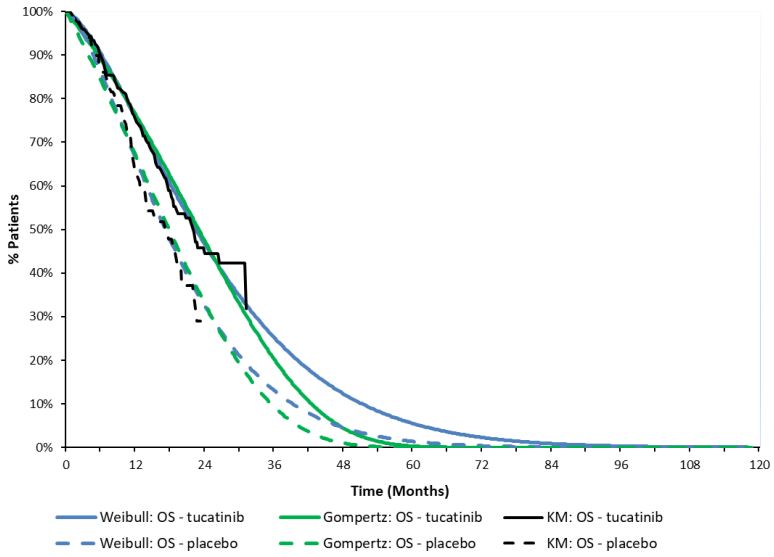
6.43 The figure shows a large step in the tucatinib OS data at around 31 months, due to the low number of patients at risk, indicating the likely unreliability of the Kaplan-Meier data at this time-point.

6.44 The ESC considered it would be more appropriate to use the Kaplan-Meier data for both PFS and OS until around 20% of patients remained at risk in each arm. The pre-PBAC response stated that there was no apparent objective basis to use Kaplan-Meier data until 20% of patients remained at risk. The PBAC acknowledged that there was no definitive cut-point at which to start the extrapolation, and noting the PBAC Guidelines v5.0 (see paragraph 6.40), recalled that it considered use of the Kaplan-Meier data until 20% of patients remained at risk was a reasonable approach in the ribociclib in combination with fulvestrant submission (paragraph 4.21, ribociclib PSD, November 2020).

6.45 Using the Weibull model to extrapolate OS, by 5 years (60 months), around 5% of patients were alive in the tucatinib arm, and 1% in the placebo arm. By the end of the model time horizon (10 years) all patients in both arms had died. The submission did not provide any external validation of the extrapolations applied in the model, in particular there was no validation investigated with real-life data.

6.46 The ESC noted that when the Gompertz model was used to extrapolate OS, as shown in the figure below, all patients in the placebo arm had died within 4.8 years, while when the Weibull model was used, all patients had died within 7.3 years. The ESC considered that the Gompertz model may be clinically plausible for the proposed population of patients with second or later-line mBC. The pre-PBAC response stated that the Weibull distribution was the best fit curve based on the AIC/BIC scores and visual inspection and that the Gompertz model did not reflect a typical shape for survival curves and did not align with the OS trend observed in the HER2CLIMB trial in which the OS curves appear to diverge from months 24 to 36.

Figure 6: OS data extrapolation - Weibull (blue lines) versus Gompertz (green lines) model



Source: 'Attachment 08 - Tucatinib mBC CEM_Final.xlsx'
KM = Kaplan-Meier; OS = overall survival

6.47 Time to treatment discontinuation (TTD) data were used to inform the duration of treatment with tucatinib, capecitabine and trastuzumab. The submission stated that TTD Kaplan-Meier estimates from the HER2CLIMB trial were used for the initial period of analysis, followed by extrapolation using survival curves. The submission did not provide the TTD Kaplan-Meier curves from the trial so this was unable to be verified during evaluation. The number of patients at risk at various time-points was unknown and thus the reliability of the Kaplan-Meier data used could not be determined. The submission selected the Gompertz parametric model to extrapolate TTD in the tucatinib arm based on visual inspection. However, the log-logistic model was associated with lower AIC/BIC scores and appeared to fit the Kaplan-Meier data more closely earlier in the curves where the data may have been more reliable. Using the Gompertz model to extrapolate TTD, the mean tucatinib treatment duration was estimated to be 11.8 months, versus a mean PFS for tucatinib of 15.4 months (while extrapolation of tucatinib treatment duration with a log-logistic model, which has a lower AIC/BIC, would result in a mean duration of 12.5 months). The ESC considered

that, given the information available, it would have been more appropriate to extrapolate TTD using the log-logistic model. The pre-PBAC response stated that the log-logistic model was not plausible for time on treatment extrapolation as it sat above the Kaplan-Meier curve for TTD beyond 15 months and therefore would overestimated patients on treatment.

6.48 The utilities applied in the base case were derived from the EQ-5D-5L data collected in the HER2CLIMB trial. Different utilities were applied in each treatment arm and in different cycles as outlined in the table below.

Table 9: Utility values used in the economic evaluation

	Tucatinib	Placebo
Base case (based on HER2CLIMB EQ-5D-5L data)		
Progression-free, cycles 1-2	0.823	0.845
Progression-free, cycles 3-4	0.835	0.835
Progression-free, cycles 5-6	0.859	0.808
Progression-free, cycles 7+	0.872	0.810
Progressed	0.738	Submission stated: 0.778 Actually applied: 0.738 (consistent with tucatinib arm)
Sensitivity analysis: Lloyd et al, 2006		
Progression-free	0.786	
Progressed	0.538	

Source: Table 3.12, pp 153-4 of the submission.

6.49 The utility values applied in the base case appeared to be overestimated and may have been unreliable because:

- As discussed in the comparative effectiveness section, EQ-5D data from the HER2CLIMB trial may not have been reliable. EQ-5D assessment was added in a protocol amendment; responses to baseline assessment were only available for 54% of patients and there was substantial missing data. The ESC also considered that patients who were less well may have been less likely to respond to the EQ-5D questionnaire, which may have biased the results (overestimated the utility values).
- The ESC considered that it was not clinically plausible for patients with second- or later-line mBC to have utility values as high as 0.872.
- Compared with the utilities from Lloyd et al, 2006 and those applied in previous PBAC submissions that included mBC health states, the utility values appeared high. The utility value used for:
  - the progression-free health state (0.808 to 0.872) was higher than previously used for first-line mBC (0.753 in the March 2020 pertuzumab submission[8]);
  - the progressed disease health state (0.738) was substantially higher than those previously used for second- or later-line progressed disease (0.55 in T-DM1 in

[8] Table 12, Pertuzumab PSD, March 2020 PBAC meeting

July 2013[9] and trastuzumab in November 2014[10]; and 0.481 in pertuzumab in March 2020[7]).

6.50 As a sensitivity analysis, the submission applied utility values from a published study by Lloyd et al, 2006 which estimated utilities for metastatic breast cancer states using hypothetical scenarios via a standard gamble task in a sample drawn from the UK general population (N = 100). The submission stated this study was selected because it was used in previous PBAC submissions that included mBC health state/s. Lloyd et al, 2006 was based on hypothetical scenarios for 'metastatic breast cancer'; it was unclear if these scenarios were applicable to the proposed population of patients with second- or later-line metastatic breast cancer, who may have a lower quality of life than patients with first-line metastatic breast cancer. Overall, the ESC considered that while the utility values derived from Lloyd et al, 2006 were more clinically plausible than the trial-based utilities, they may still overestimate quality of life in this patient population. Although the pre-PBAC response noted that the model results are not sensitive to the progressed state utility values, the PBAC considered that the values applied were not clinically plausible.

6.51 Table 10 summarises the incremental costs for health care resource items used in the economic evaluation.

Table 10: Health care resource items: disaggregated summary of cost impacts (discounted)

Resource item	Tucatinib cost	Placebo cost	Incremental cost	% of total incremental cost
Pharmaceutical products				
Tucatinib	$	$0	$	93%
Capecitabine + trastuzumab + administration cost	$	$13,254	$	7%
Health state costs				
Progression-free health state	$	$971	$	1%
Progressed disease health state	$	$1,211	-$	0%
End of life costs	$	$12,665	-$	0%
Management of adverse events				
Loperamide (anti-diarrhoeals)	$	$6	$	0%
Adverse event hospitalisations	$	$738	$	1%
Post-progression costs				
Subsequent therapies	$	$10,987	-$	0%
Total				
Total costs	**$**	**$39,830**	**$**	**100%**

Source: Table 3.32 of the submission.

6.52 Tucatinib drug costs accounted for 93% of the total incremental costs. While the submission likely underestimated the cost of subsequent therapies and health state costs, this had little impact on the results of the model.

[9] Section 10, T-DM1 PSD, July 2013 PBAC meeting

[10] Paragraph 6.49, Trastuzumab PSD, November 2014 PBAC meeting

6.53 Tucatinib drug costs were calculated based on the cost per milligram ($[redacted] per mg) for the average dose per patient in the HER2CLIMB trial (266 mg per dose, based on 88.5% dose intensity). Use of the cost per milligram, rather than the cost per whole tablet likely underestimated drug costs as the submission did not apply a flat price per milligram for the 50 mg and 150 mg tablets. The ESC considered that it would have been more reasonable to calculate tucatinib drug costs based on the cost per whole tablet using the actual doses received in the trial.

6.54 The table below summarises the key drivers of the model.

Table 11: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained.
Utilities	Based on HER2CLIMB EQ-5D-5L data in the base case. These utilities appeared to be overestimated and may have been unreliable.	High, favours tucatinib. Use of utilities by Lloyd et al, 2006 increased the ICER to $[redacted][1]/QALY gained.
Duration of use of Kaplan-Meier data	Median follow-up in the HER2CLIMB trial was 10.4 months and 14 months for PFS and OS, respectively. Kaplan-Meier data were used in the model until 31 and 23 months for the tucatinib and placebo arms, respectively for OS. At these time-points very few patients remained at risk (fewer than 10 patients in the tucatinib arm), and these data were likely unreliable at these late time-points.	High, favours tucatinib. Use of Kaplan-Meier data until 20% of patients were at risk in each arm (for PFS and OS) increased the ICER to $[redacted][1]/QALY gained.
Extrapolation of OS	The ESC considered that the submission's use of the Weibull model to extrapolate OS may be optimistic, and considered that the Gompertz model may be clinically plausible. Combined with extrapolation from earlier time-points (as discussed above), the use of the Gompertz model increased the ICER significantly.	High, favours tucatinib. Use of Gompertz to extrapolate OS increased the ICER to $[redacted][1]/QALY gained. Use of Gompertz to extrapolate OS + use of Kaplan-Meier data until 20% of patients were at risk (for PFS and OS) increased the ICER to $[redacted][2]/QALY gained.
Tucatinib drug costs	Tucatinib drug costs accounted for 93% of the total incremental costs. Tucatinib drug costs were calculated based on the cost per milligram for the average dose per patient in the HER2CLIMB trial, rather than the cost per whole tablet that was used.	Moderate, favours tucatinib. Assuming patients use whole tablets increased the ICER to $[redacted][3]/QALY gained.
Extrapolation of TTD in the tucatinib arm	The Gompertz parametric function was used to extrapolate time on treatment in the tucatinib arm based on visual inspection. However, the log-logistic function was associated with lower AIC/BIC scores and appeared to fit the Kaplan-Meier data more closely earlier in the curves where the data may have been more reliable. The TTD Kaplan-Meier curves from the trial were not provided in the submission. In the tucatinib arm, Kaplan-Meier data were used until 31 months however the number of patients remaining at risk at this time-point was unclear and thus the reliability of the Kaplan-Meier data used could not be determined.	Moderate, favours tucatinib. Use of the log-logistic function increased the ICER to $[redacted][3]/QALY gained. Use of the log-logistic function plus changing the time-point until which Kaplan-Meier data were used increased the ICER to $[redacted][3]/QALY gained.

Source: Compiled during evaluation.

AIC = Akaike information criteria; BIC = Bayesian information criteria; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

The redacted values correspond to the following ranges:

[1] *$255,000 to < $355,000/QALY gained*

[2] *$355,000 to < $455,000/QALY gained*

[3] $255,000 to < $355,000/QALY gained

6.55 The results of the stepped economic evaluation are outlined in the table below.

Table 12: Results of the stepped economic evaluation

Step and component	Tucatinib	Placebo	Increment
Step 1: Trial-based costs and outcomes: based on first-line drug and administration costs			
Costs	$[redacted]	$14,949	$[redacted]
Progression-free years gained	0.985	0.582	0.403
LYG	1.731	1.297	0.434
Incremental cost/extra progression-free year gained			$[redacted][1]
Incremental cost/extra LYG			$[redacted][1] /LYG
Step 2: Cost of AEs and death included			
Costs	$[redacted]	$29,241	$[redacted]
LYG	1.731	1.297	0.434
Incremental cost/extra life year gained			$[redacted][1] /LYG
Step 3: Utilities included			
Costs	$[redacted]	$29,241	$[redacted]
QALY	1.406	1.030	0.375
Incremental cost/extra QALY gained			$[redacted][1] /QALY
Step 4: Base case: Extrapolation to 10 year time horizon, drug costs based on extrapolated time to treatment discontinuation, incorporating health state costs and post-progression anti-cancer treatments, including discounting			
Costs	$[redacted]	$39,830	$[redacted]
LYG	2.06	1.56	0.50
QALYs	1.673	1.208	0.465
Incremental cost/extra LY gained			$[redacted][1] /LYG
Incremental cost/extra QALY gained (base case)			$[redacted][1] /QALY

Source: Table 3.31, p170 of the submission.
LYG = life years gained; QALY = quality-adjusted life-year
The redacted values correspond to the following ranges:
[1] $255,000 to < $355,000/QALY gained

6.56 The extrapolation of treatment benefits beyond the clinical trial data had the largest impact on the stepped economic evaluation. While Step 4 included the incorporation of multiple steps (extrapolation to a 10 year time horizon, basing drug costs on extrapolated time to treatment discontinuation, incorporation of health state costs and post-progression anti-cancer treatments, and applying discounting), extrapolation was the only component that had an impact on this step. The inclusion of health state costs and post-progression anti-cancer treatment costs only changed the ICER by $0 to < $5,000/QALY gained.

6.57 Based on the economic model presented in the submission, treatment with tucatinib (+ capecitabine + trastuzumab) was associated with a cost per QALY gained of $255,000 to < $355,000 compared with placebo (+ capecitabine + trastuzumab). This ICER was likely underestimated due to: the use of utility values that appeared to be unreliable and overestimated; overestimation of OS due to the use of Kaplan-Meier data until very few patients remained risk and the use of an optimistic extrapolation function; and underestimation of tucatinib drug costs.

6.58 The results of key sensitivity analyses presented in the submission and conducted during evaluation are summarised below.

Table 13: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	**$** [redacted]	**0.46**	**$** [redacted] 1
Brain metastases population	$ [redacted]	0.47	$ [redacted] 1
Time horizon (base case: 10 years)			
• 3 years	$ [redacted]	0.31	$ [redacted] 2
• 5 years	$ [redacted]	0.43	$ [redacted] 1
OS extrapolation (base case: Weibull)			
• Log-logistic	$ [redacted]	0.50	$ [redacted] 1
• Gompertz	$ [redacted]	0.39	$ [redacted] 1
• Generalised gamma	$ [redacted]	0.47	$ [redacted] 1
Treatment discontinuation (base case: based on TTD, Gompertz extrapolation in tucatinib arm, no extrapolation in placebo arm)			
• Based on PFS	$ [redacted]	0.46	$ [redacted] 1
• Log-logistic in tucatinib arm (lower AIC/BIC than Gompertz)	$ [redacted]	0.46	$ [redacted] 1
• Weibull in tucatinib arm (lower AIC/BIC than Gompertz)	$ [redacted]	0.46	$ [redacted] 1
Utilities (base case: HER2CLIMB trial; PFS: 0.808 to 0.872; PD: 0.738)			
• Lloyd 2006 (PFS: 0.786 PD: 0.538; same utility applied to each arm)	$ [redacted]	0.40	$ [redacted] 1
Tucatinib drug costs (based on per mg basis; tucatinib cost per cycle: $7,184)			
• Assuming patients use full tablets ($7,593.69 per cycle)	$ [redacted]	0.46	$ [redacted] 1
OS extrapolation – point until which Kaplan-Meier data are used (base case: 135 and 101 weeks)			
• 20% *of patients remain* at risk in each arm (78 weeks in the tucatinib arm and 72 weeks in the placebo arm)	$ [redacted]	0.41	$ [redacted] 1
PFS extrapolation – point until which Kaplan-Meier data are used (base case: 135 weeks and 86 weeks)			
• 20% *of patients remain* at risk in each arm (46 weeks in the tucatinib arm and 37 weeks in the placebo arm)	$ [redacted]	0.44	$ [redacted] 1
Multivariate analyses			
A = OS and PFS extrapolation – use Kaplan-Meier data until 20% of patients remain at risk for both PFS and OS	$ [redacted]	0.39	$ [redacted] 1
B = Treatment discontinuation extrapolation: • using log-logistic in both arms and • extrapolated from 78 weeks in the tucatinib arm and 72 weeks in the placebo arm (per 'OS extrapolation' sensitivity analysis).	$ [redacted]	0.46	$ [redacted] 1
Lloyd 2006 utilities + tucatinib drug costs based on full tablets	$ [redacted]	0.40	$ [redacted] 1
PFS: • Extrapolation after 20% of patients at risk in each arm and • Lloyd 2006 utilities (which have a more plausible difference between PFS and PD utilities)	$ [redacted]	0.35	$ [redacted] 2
A + Lloyd 2006 utilities + tucatinib drug costs based on full tablets	$ [redacted]	0.31	$ [redacted] 2
A + Gompertz model for OS	$ [redacted]	0.31	$ [redacted] 2
A + B + Lloyd 2006 utilities + tucatinib drug costs based on full tablets	$ [redacted]	0.31	$ [redacted] 3
A + B + Gompertz model for OS + Lloyd 2006 utilities + tucatinib drug costs based on full tablets	$ [redacted]	0.25	$ [redacted] 4

Source: Table 3.4.1 of the submission. *Analyses in italics were conducted during evaluation.*

AIC = Akaike information criteria; BIC = Bayesian information criteria; ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressed disease; PFS = progression-free survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

The redacted values correspond to the following ranges:
[1] $255,000 to < $355,000/QALY gained
[2] $355,000 to < $455,000/QALY gained
[3] $455,000 to < $555,000/QALY gained
[4] $555,000 to < $655,000/QALY gained

6.59 The submission presented the results of a scenario analysis of the brain metastases population, which resulted in an ICER of $255,000 to < $355,000/QALY gained. The scenario analysis used the same methods as the base case model but used subgroup data from the brain metastases population in HER2CLIMB for OS, PFS, adverse events and utilities. There were significant issues with the utility data applied, due to the aforementioned issues which would likely be exacerbated by the smaller size of the brain metastases population. The impact of tucatinib on the quality of life of patients with brain metastases was unclear.

6.60 Changes to PFS extrapolation only had a minor impact on the model results, likely due to the relatively small difference between the progression-free and progressed disease health states applied in the base case (0.078 based on the average utilities of 0.836 and 0.758 in the two health states). When utilities with a more plausible difference between the health states were applied, the model became more sensitive to changes in PFS extrapolation.

6.61 The ESC noted the following sensitivity analyses, applied as multivariate analyses in a step-wise manner, increased the ICER from $255,000 to < $355,000/QALY (with 0.50 incremental life years gained (LYG)) to:

- Applying the Lloyd 2006 utilities: $255,000 to < $355,000/QALY;
- Above plus basing the tucatinib drug costs on full tablets: $255,000 to < $355,000/QALY;
- Above plus using the Kaplan-Meier data until 20% of patients remain at risk for both PFS and OS: $355,000 to < $455,000/QALY (resulting in 0.42 LYGs); and
- Above plus changing the treatment discontinuation extrapolations (using log-logistic model, and extrapolating from an earlier time-point): $455,000 to < $555,000/QALY.

This indicative multivariate analysis resulted in a QALY gain of only 0.31 over 10 years and 0.42 LYG over 10 years versus 0.43 LYG in the trial-based analysis (i.e. Step 1 of the stepped economic evaluation).

6.62 The ESC further noted that the above indicative multivariate analysis plus extrapolating OS using the Gompertz model resulted in an ICER of $555,000 to < $655,000/QALY. This resulted in a QALY gain of only 0.25 over 10 years and LYG of 0.32 over 10 years versus 0.43 in the trial-based analysis, which may be overly conservative, given the clinical data. However, the ESC considered that the Lloyd et al, 2006 utilities may still overestimate quality of life in this patient population.

6.63 The PBAC had previously considered that pertuzumab and T-DM1 in mBC were reasonably cost-effective with ICERs in the range of $45,000 to $75,000 per QALY (para

7.20 and 7.29, Pertuzumab, Trastuzumab and T-DM1 PSD, November 2014 PBAC meeting).

Tucatinib cost/patient/course: $[redacted]

Table 14: Drug cost per patient for tucatinib

	Tucatinib Trial dose and duration	Tucatinib Model	Tucatinib Financial estimates
Recommended dose	300 mg twice daily	300 mg twice daily	300 mg twice daily
Dose intensity	88.5%	88.5%	88.5%
Total mg administered per 21-day cycle	11,151 mg	11,151 mg	10,321 mg[c]
Cost per mg	$[redacted] per mg [a]	$[redacted] per mg [a]	$[redacted] per mg
Cost/patient/ 21-day cycle	$[redacted]	$[redacted]	$[redacted]
Mean duration	10.9 cycles [b]	17 cycles	17 cycles
Cost/patient/course	$[redacted]	$[redacted]	$[redacted]

Source: compiled during evaluation based on: Table 13 of the CSR;
[a] Based on 150 mg tablet
[b] Based on truncated mean reported in trial
[c] Based on a weighted average of 81.4% of patients getting 300x2x21x0.885 and 18.6% getting 1.8x50x4x21x0.885. These values have not been updated to adjust for changes proposed in the PSCR.
[d] Based on the cost / (scripts x mg per script)

6.64 The economic model estimated that tucatinib would cost $[redacted] per patient (undiscounted). This assumed a dose intensity of 88.5%, and was calculated based on the cost per milligram, rather than the cost per whole tablet, which underestimated the likely cost of tucatinib.

6.65 As the treatment duration was longer in the tucatinib arm than the placebo arm, the cost of capecitabine and trastuzumab would be higher when used in combination with tucatinib. The economic model estimated that the total cost of capecitabine and trastuzumab would be:

- $[redacted] in the tucatinib arm; and
- $11,618 in the placebo arm.

Estimated PBS usage & financial implications

6.66 This submission was not considered by DUSC. The submission used a pharmacoepidemiological approach to estimate the number of treated patients. The majority of assumptions used to estimate the number of eligible patients were from a PBS 10% sample from Tableau online (Model Solutions).

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent population	Number of prevalent patients based on 10% sample analysis	Potentially unreliable and likely overestimated due to the extrapolation method.
Patients who progress to second line treatment	23.3% based on the 10% sample analysis	Could be under or overestimated, the 10% sample included too few patients for it to be a reliable source
Patients who are second line or third line with prior T-DM1	64.4% based on the 10% sample analysis, an Australian abstract (Lee) and the Public Summary document for T-DM1 in adjuvant treatment	Could be under or overestimated, the 10% sample included too few patients for it to be a reliable source
Uptake rate	55% in Year 1 increasing to 80% in Year 6. Based on sponsor's assumption.	Likely underestimated in the true eligible population because patients are likely to add tucatinib to later line treatments
Proportions of patients continuing treatment after initial 12 weeks of treatment	83% from HER2CLIMB clinical trial (based in the PFS rate at 3 months)	-
Duration	11.75 months from HER2CLIMB clinical trial	This was consistent with the economic evaluation (equivalent to 17 x 21-day cycles)

Source: Table 4.3, p183; Table 4.4, p184; Table 4.5, p185; Table 4.6, p185 of the submission.
PFS = progression free survival; T-DM1 = ado-trastuzumab emtansine

6.67 The estimated use and financial implications are shown in the table below. The estimates in the table below include the PSCR's corrections to account for an issue identified during evaluation regarding the calculation of the number of scripts required for dose reductions. However, it was unclear if these calculations adequately accounted for patients who discontinued tucatinib due to an adverse event.

Table 16: Estimated use and financial implications, *as updated in the PSCR*

	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][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][5]

Source: Table 4.6 of the submission; Table 4.8 of the submission; Table 4.13 of the submission; Tables 3-4 of the PSCR.
PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
[a] Assuming 25.4 doses per week for 150 mg pack and 25.2 doses per week for 50 mg tablets as estimated by the submission.
Figures in italics were provided as corrections in the PSCR.
The redacted values correspond to the following ranges:
[1] <500
[2] 500 to < 5,000
[3] $10 million to < $20 million
[4] $20 million to < $30 million
[5] $30 million to < $40 million

6.68 The total cost to the PBS/RPBS of listing tucatinib was estimated to be $30 million to < $40 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing.

6.69 The PBS 10% sample data were not a sufficiently reliable basis for estimating the eligible population as:

- the sample included too few patients for it to be a reliable source for estimating the number of metastatic patients or the proportion of these patients eligible under the proposed clinical treatment algorithm. For example, the number of mBC patients in the 10% sample decreased in 2018 and 2019, while this trend was not observed in the full PBS data.
- the included item codes may have overestimated the number of metastatic patients as they may have included PBS listings for early and locally advanced breast cancer.
- patients were counted as being 'on therapy' if they were supplied a script in the previous three months, which may overestimate the number of patients on treatment at a time, as most breast cancer regimens are given every three weeks.

6.70 An analysis of the full PBS data (which were accessed by the Department of Health in an analysis conducted during evaluation) indicated the number of eligible patients was overestimated. The PBAC noted that the use of data from the full PBS data set, as provided in the Table 17, may provide a more reliable approach to estimate the eligible population. The proposed population would need to account for the increasing number of patients who are likely to be treated with T-DM1 in the adjuvant setting which, in turn, is likely to reduce the number of patients progressing to later line treatments.

Table 17: Analysis of the full PBS data set

Year	Initiated pertuzumab[a]	Initiated T-DM1[a]	Metastatic treated patients[b]	Tucatinib eligible patients[b]
2016	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][1]
2017	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][1]
2018	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][1]
2019	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][1]
2020	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][1]

Source: Data extracted from January 2014 to December 2020
PBS = Pharmaceutical Benefits Scheme; T-DM1 = ado-trastuzumab emtansine
[a] Any initiation, not first initiation i.e. patients may be counted in both of these columns
[b] Patients treated with trastuzumab, pertuzumab, T-DM1 or lapatinib for metastatic disease
[c] Patients with metastatic disease who have previously received T-DM1 and were treated in third or later line with trastuzumab or lapatinib
The redacted values correspond to the following ranges:
[1] <500
[2] 500 to < 5,000

6.71 The submission's use of linear extrapolation was also likely to have overestimated the number of eligible patients. Full PBS data showed that the total number of metastatic patients is growing at a slower but constant rate.

6.72 The submission applied uptake rates of 55% in Year 1, growing to 80% in Year 6. This was likely underestimated.

6.73 A compliance rate of 88.5% was assumed for all patients, sourced from the dose intensity In the HER2CLIMB trial. The application of the compliance rate and dose reductions may have underestimated the number of supplied scripts.

6.74 The submission did not include grandfathered patients.

Financial Management – Risk Sharing Arrangements

6.75 The submission did not propose a risk sharing arrangement.

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

7 PBAC Outcome

7.1 The PBAC did not recommend tucatinib, in combination with trastuzumab and capecitabine, for the treatment of HER2-positive (HER2+) metastatic breast cancer (mBC), including patients with brain metastases. The PBAC noted that tucatinib provided a clinical benefit in terms of progression free survival (PFS) and overall survival (OS) and acknowledged the 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. The PBAC also considered that the number of treated patients was likely overestimated.

7.2 The PBAC noted the consumer comments which supported the listing of tucatinib for the treatment of HER2+ mBC, and in particular for patients with brain metastases.

7.3 The PBAC considered that the places in therapy for tucatinib in combination with trastuzumab and capecitabine for the treatment of HER2+ mBC, (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 or as second-line treatment in patients who have progressed following treatment with one prior line of HER2-directed agents for metastatic disease and T-DM1 for the treatment of either adjuvant or metastatic disease), were appropriate.

7.4 The PBAC considered that the nominated comparator of trastuzumab plus capecitabine was appropriate.

7.5 The PBAC noted that the submission was based on the results of one randomised controlled trial, HER2CLIMB, which compared treatment with tucatinib plus trastuzumab and capecitabine with placebo plus trastuzumab and capecitabine in patients with HER2+ mBC who had received prior therapy for metastatic disease. The PBAC noted that patients with brain metastases comprised 48% of the total HER2CLIMB population.

7.6 The PBAC noted that only 6% of patients in the HER2CLIMB trial had received tucatinib as a second-line metastatic treatment. The PBAC considered that tucatinib use in this population in clinical practice would likely be higher due to the use of T-DM1 in the

adjuvant setting, which was not standard practice at the time HER2CLIMB was conducted.

7.7 The PBAC noted that tucatinib resulted in a statistically significant improvement in PFS (HR = 0.54; 95% 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.

7.8 The PBAC 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 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).

7.9 The PBAC 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.

7.10 With regards to safety, the PBAC noted that the nature of the adverse events reported in the two arms of the HER2CLIMB trial were similar, with higher rates reported in the tucatinib arm. The PBAC 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.

7.11 Overall, the PBAC considered that tucatinib was inferior to placebo in terms of comparative safety.

7.12 The PBAC noted that the submission presented a cost utility analysis comparing tucatinib plus trastuzumab and capecitabine with placebo plus trastuzumab and capecitabine. The PBAC considered that the resultant ICER of $255,000 to < $355,000 per QALY was high and highly uncertain.

7.13 The PBAC noted the following issues with the economic model:

- The application of a 10 year time horizon. The PBAC considered that for patients with mCB, and particularly those with brain metastases, a five year time horizon would be more appropriate;
- The utilities applied in the model. The PBAC noted that the trial-based utility values were not informative as collection of quality of life 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 noted that the utility values were higher than those reported in the literature and applied in previous PBAC submissions for mBC. The PBAC considered that the utility values derived from Lloyd et al, 2006 were more clinically plausible;
- The tucatinib drug costs applied in the model. The PBAC 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. In addition, the PBAC noted that the submission did not apply a flat price per milligram across the 50 mg and 150 mg strengths (the cost of the 50 mg tablet per milligram was higher). The PBAC considered that a flat price per milligram should be used and with tucatinib drug costs based on the cost per whole tablet received;

- Uncertainties relating to the point of extrapolation of the PFS and OS curves. The PBAC considered that Kaplan-Meier data should be used until approximately 20% of patients remained at risk in each arm;
- Uncertainties relating to the goodness of fit of the time to treatment discontinuation curve.

7.14 The PBAC noted that a multivariate analysis adjusting for all of the above factors, except the time horizon, potentially underestimated the benefit of tucatinib (see paragraph 6.61). The PBAC considered that a scenario in which the time horizon, utilities and costing of tucatinib were revised would be a reasonable base case scenario (ICER = $355,000 to < $455,000 per QALY). Noting that previous treatments for mBC had been recommended with ICERs in the range of $45,000 to $75,000 per QALY and the effectiveness of tucatinib in patients with brain metastases, the PBAC considered that an ICER of $75,000 to < $95,000 per QALY would be reasonable.

7.15 The PBAC 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 the linear extrapolation applied to the estimated number of metastatic patients overestimated the population and that the uptake rate was likely underestimated.

7.16 The PBAC recalled that the T-DM1 trastuzumab emtansine 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 (see Table 17).

7.17 The PBAC considered the outstanding issues may be addressed in a simple resubmission for tucatinib if the following changes were made, without any additional amendments, to the -

1) economic evaluation:
   - application of a five year time horizon;
   - application of utility values from Lloyd et al, 2006;

- use of a flat price per milligram for tucatinib across the 50 mg and 150 mg strengths and application of the distribution of doses from the trial; and
- a price reduction resulting in an ICER of $75,000 to < $95,000 per QALY.

2) utilisation and financial impact estimates:

- patient numbers based on those who initiated T-DM1 treatment before the adjuvant T-DM1 listing was available, i.e. April 2020, and then uptake rates applied to determine the tucatinib patient population.

7.18 The PBAC considered that an Early Re-Entry pathway would be acceptable if the resubmission addressed each of the points in the above paragraph with no further adjustment. The resubmission must be lodged by Week 7 of the current PBAC cycle or the next cycle. If any of these terms are not acceptable to the sponsor, a Standard Re-Entry pathway is available.

7.19 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.