7.06 NERATINIB, Tablets 40 mg, Nerlynx®, Specialised Therapeutics PM Pty Ltd.

1 Purpose of Application

1.1 The resubmission requested an Authority Required listing for neratinib for extended adjuvant treatment of adult patients with human epidermal growth factor receptor-2 positive (HER2+), hormone receptor positive (HR+), early breast cancer (eBC) who have completed prior adjuvant trastuzumab-based therapy within the past 12 months. The PBAC previously considered neratinib in this indication at its March 2019 meeting.

1.2 The basis of the requested listing was cost-effectiveness of neratinib compared to placebo. This is unchanged from the original submission. The resubmission also included pertuzumab as a near market comparator.

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

Component	Description
Population	Adult patients with HER2+, HR+, eBC who have completed prior adjuvant trastuzumab based therapy within the past 12 months
Intervention	Neratinib
Comparator	Main comparator: usual care/placebo Near market comparator: pertuzumab
Outcomes	Invasive disease-free survival (primary outcome), distant disease-free survival, time to distant recurrence, incidence of CNS recurrence, adverse events
Clinical claim	In adult patients with early-stage HER2-overexpressed/amplified, hormone positive breast cancer who have received prior adjuvant trastuzumab based therapy, neratinib is more effective than placebo at improving invasive disease-free survival.

CNS: central nervous system, HER2+: human epidermal growth factor receptor 2 positive; HR+: hormone receptor positive; eBC: early breast cancer
Source: Table 15, p49 of the resubmission.

2 Requested listing

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

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
NERATINIB 40 mg tablet	180	~~1 (initial)~~ ~~4 (continuing)~~ *2*	$[redacted]	Nerlynx, Therapeutics PM

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	*Early*
Condition:	HER2 positive breast cancer [14765]
PBS Indication:	Early HER-2 positive breast cancer [7754]
Treatment phase:	~~Initial~~ *Adjuvant* treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Streamlined
Clinical criteria:	*The treatment must be adjuvant to surgery followed by adjuvant therapy with trastuzumab* [new concept] AND Patient must have ~~been treated with~~ *completed* a course of adjuvant trastuzumab within ~~the last~~ 12 months prior to initiating treatment with this drug for this condition. [new concept] ~~OR~~ ~~Patient must have discontinued treat[ment] with a course of adjuvant T-DM1 or trastuzumab plus pertuzumab within 6 months of initiating treatment with this drug for this condition AND Patient must have subsequently been treated with a course of adjuvant trastuzumab within the last 12 months prior to initiating treatment with this drug for this condition~~ AND Patient must not have local or regional recurrence of disease or metastatic disease [new concept] AND The condition must be hormone receptor positive [10652] AND The treatment must be the sole PBS-subsidised anti-HER-2 therapy [15452] AND Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy ~~for this drug for this condition~~ [7746]
Prescriber Instructions:	~~Anti-diarrhoeal prophylaxis is recommended during the first 2 cycles (56 days) of treatment and should be initiated with the first dose of neratinib.~~ A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. [11473]

Administrative Advice:	~~No applications for increased maximum quantities will be authorised.~~ *No increase in the maximum quantity or number of units may be authorised.* [7606] ~~No applications for increased repeats will be authorised.~~ *No increase in the maximum number of repeats may be authorised.* [7607]

2.2 The proposed restriction was updated in the resubmission and is mostly consistent with the PBAC and Secretariat suggestions (neratinib Public Summary Document (PSD), March 2019).

- The proposed initial restriction was updated to be 'Authority Required (Telephone)' listing to align with the initial restriction for trastuzumab for eBC.
- The proposed initial restriction was updated to include prescriber instructions to initiate anti-diarrhoeal prophylaxis (loperamide, PBS item 10889D) with the first dose of neratinib and ongoing during the first three cycles (56 days of treatment). The Economics Sub-Committee (ESC) considered this was appropriate.
- The proposed restriction was updated to limit the use of neratinib following trastuzumab monotherapy. The resubmission stated that 'If trastuzumab emtansine (T-DM1) and/or pertuzumab (T+Ptz +Chemo) were to be listed in early stage breast cancer, patients receiving these therapies will not be permitted to receive neratinib in the proposed indication' (p2 of the resubmission).
- The Secretariat proposed that one restriction to cover initial, continuing and grandfathered patients would be appropriate, given the absence of requirements to meet or demonstrate objective response criteria to continue treatment. Additionally, grandfathered patients would qualify for PBS-subsidised treatment under the proposed restriction without any need for treatment interruption. A maximum of 2 repeats would reflect clinical monitoring requirements for patients in this extended adjuvant phase of treatment.

2.3 The ESC noted there were differences in the clinical algorithm, TGA indication, proposed PBS listing and the populations in the ExteNET trial. Table 2 compares these differences.

Table 2: Summary of factors in the ExteNET trial versus the proposed PBS listing

	Clinical algorithm	TGA indication	Proposed restriction	ExteNET trial
Prior neoadjuvant treatment				
Residual disease	No	Yes	Yes (HR+ only)	Yes
pCR				
HR+	Yes	Yes	Yes	No
HR-	No	Yes	No	No
Adjuvant treatment only				
HR+	Yes	Yes	Yes	Yes
HR-	No	Yes	No	Yes

pCR: Pathological Complete Response; HR+: hormone receptor positive; HR-: hormone receptor negative
Complied during the evaluation

2.4 The proposed PBS indication only included patients with HR+ disease. This is not consistent with the ExteNET trial (ITT and amended intend to treat (aITT) population) or the TGA indication which include patients with both HR+ and HR- disease.

2.5 The requested restriction was not consistent with the clinical algorithm presented, in that patients with residual disease following neoadjuvant treatment are expected to be treated with T-DM1 but are not excluded under the proposed restriction. The requested restriction was not consistent with the population in the ExteNET trial, in that patients with pCR following neoadjuvant treatment and patients with node negative stage 1 disease were excluded after protocol amendment 3 but are not excluded from treatment under the proposed restriction.

2.6 The resubmission included a revised clinical management algorithm incorporating the likely clinical place of emerging therapies pertuzumab and T-DM1. The resubmission also claimed that patients unable to tolerate T-DM1 or pertuzumab would discontinue treatment without completing a full treatment course and would continue treatment with trastuzumab alone. T-DM1 and pertuzumab are currently not listed on the PBS for the treatment of HER2+, eBC. However, the resubmission stated that 'should these agents be listed on the PBS in future, the wording of the neratinib restriction should not preclude its use by these patients who have needed to discontinue adjuvant T-DM1 or pertuzumab' (p67 of the resubmission). The ESC considered that this was problematic given that there is no clinical evidence of the effectiveness and safety of switching treatment from T-DM1/pertuzumab to trastuzumab for less than 12 months and followed with neratinib.

2.7 The resubmission noted that the Nerlynx Access Program (NAP) commenced in September 2018 and estimated that approximately 509 patients will be initiated through grandfathering if neratinib was listed on the PBS in 2020 Q2. The Pre-PBAC response noted that 158 oncologists have prescribed neratinib for almost 300 patients on the NAP. The original submission estimated 120 to 180 patients would be initiated through grandfathering.

2.8 The ESC noted the ExteNET trial included patients who were immunohistochemistry (IHC3+) or in situ hybridization (ISH+) for HER2. However, in the Australia population,

trastuzumab (for eBC) is reimbursed under the condition of patients having completed only ISH test.

2.9 The resubmission proposed a higher dispensed price ($[redacted]) compared with the original submission ($[redacted]).

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

3 Background

Registration status

3.1 The original submission was made under TGA/PBAC Parallel Process. The TGA Clinical Evaluation Report (Round 1) was available at the time of consideration by the PBAC in March 2019.

3.2 Neratinib was approved by the TGA on 14th March 2019 for the following indication:

Neratinib is indicated for the extended adjuvant treatment of adult patients with early-stage HER-2- overexpressed/amplified breast cancer, to follow adjuvant trastuzumab based therapy.

Previous PBAC consideration

3.3 The PBAC previously considered neratinib at its March 2019 meeting and did not recommend the listing of neratinib for the treatment of adult patients with HER2 +, HR+, eBC who have completed prior adjuvant trastuzumab based therapy within the past 12 months.

3.4 The PBAC previously considered that the clinical place for neratinib is unclear given the changing treatment landscape of early stage HER-2 positive breast cancer, emerging therapies, and the small and uncertain benefit of neratinib balanced against the substantial risk of adverse events, in particular severe diarrhoea. The PBAC considered the economic analysis presented to be highly uncertain, and the uptake and financial estimates to be overestimated (paragraph 7.1, neratinib PSD, March 2019).

3.5 Overall, the ESC advised that the PBAC's key concerns with the March 2019 submission were not addressed by the resubmission, and the resubmission introduced additional areas of uncertainty. The PBAC agreed with the ESC and considered the main outstanding matters of concern include:

- The clinical place in therapy of neratinib with other adjuvant treatment of HER2+ HR+ eBC is still unclear and inconsistent throughout the resubmission.

- Clinical data remained unchanged from the previous submission and no OS data were provided as requested by PBAC. Therefore, uncertainties regarding the clinical claim remained.
- Although the documentation provided with the model was improved from the original submission and some of the PBAC's concerns with the model were addressed, some issues were not addressed by the resubmission. Changes to the model structure, assumptions, inputs and inconsistency with the clinical algorithm introduced additional uncertainty to the economic evaluation.
- The uptake and financial estimates were still considered to be overestimated.

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

4 Population and disease

4.1 The population and disease were unchanged from the original submission.

4.2 The resubmission stated that the current treatment for women with HER2+, eBC is complete surgical excision followed by 1 year of trastuzumab in combination with chemotherapy (T+Chemo). At the time of evaluation, trastuzumab was PBS listed for adjuvant or neoadjuvant therapy for HER2+, eBC. The ESC noted that the use of trastuzumab in the neoadjuvant setting in Australia for eBC aligns with the neoadjuvant trastuzumab approach allowed in the ExteNET trial.

4.3 The ESC noted that the previous submission proposed the listing of neratinib on the PBS as an additional line of therapy for adult patients with HER2+, HR+, eBC who have been treated with trastuzumab-based therapy within the past 12 months. The ESC noted that the current clinical guidelines for adjuvant HR+, HER2+ BC advise considering extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR+, HER2+ disease with a perceived high risk of recurrence[1]. The ESC considered that it would not be appropriate to treat all HER2+, HR+ eBC patients with extended adjuvant treatment. The ESC noted it was uncertain whether (if PBS listed) use of pertuzumab would negate the clinical benefit of neratinib in this population and noted this was appropriately revised in the resubmission's proposed clinical algorithm.

4.4 The resubmission presented a new clinical management algorithm (Figure 1) that included emerging treatments (T-DM1 and pertuzumab) and defined the position of neratinib within the HER2+, eBC treatment pathway as per the PBAC recommendation (paragraph 7.5, neratinib PSD, March 2019). Pertuzumab has been considered previously by the PBAC in July 2018 and March 2019, however both submissions were rejected. T-DM1 was considered by the PBAC at the November 2019 meeting.

[1] *National Comprehensive Cancer Network Guidelines Version 3.2019 Invasive Breast Cancer*

4.5 The ESC noted that the clinical management algorithm in the resubmission did not align with the proposed restrictions, the key pivotal trial (ExteNET), the economic model nor the estimated use and financial costs. Overall, the ESC considered that there was no further clarity around the clinical place of neratinib in the resubmission due to these inconsistencies. The ESC considered that the lack of clarity around the clinical place in therapy for neratinib was also a fundamental issue for determining its cost effectiveness in eBC compared to other likely treatments for this patient group.

4.6 A summary of the different treatment pathways for eBC and the potential populations within these pathways was provided with the pre-PBAC response. A summary of the potential populations and issues identified by the PBAC is presented in Table 3.

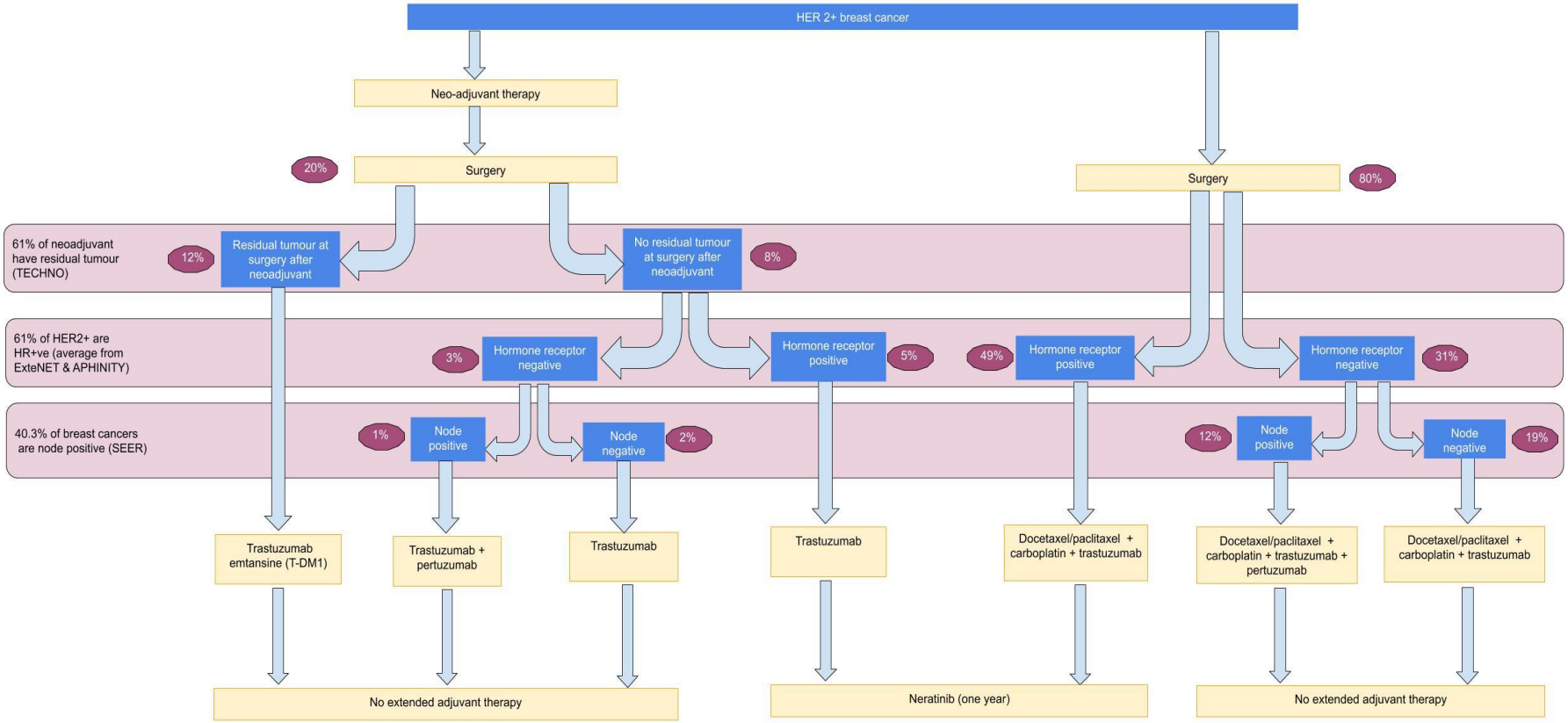
Table 3: Potential populations noted in resubmission and summary of issues

	Potential populations	Issues identified by the PBAC
Neoadjuvant pathway	Patients with residual disease post neoadjuvant therapy	Patients should receive TDM1 if available, based on efficacy shown in the KATHERINE trial There is no evidence for neratinib post T-DM1
	Patients with residual disease post neoadjuvant therapy, who discontinue adjuvant T-DM1	9.6%* of patients switched to trastuzumab in the KATHERINE trial There is no evidence for neratinib in patients who discontinue adjuvant T-DM1
	Prevalent patients with residual disease currently on adjuvant trastuzumab.	If T-DM1 is listed this will be a diminishing population
	Patients with a pCR	Low likelihood of benefit as patients are at lower risk of recurrence There is a paucity of evidence for neratinib in this population as patients with a pCR after neoadjuvant therapy were excluded from the ExteNET trial following protocol amendment 3
Adjuvant pathway	T1a/bN0 tumours	There is no data in this population as patients were excluded from ExteNET study
	T1cN0 tumours	There is a paucity of data for neratinib in this population as patients were excluded from the ExteNET trial following protocol amendment 3.
	≥T1cN0-3 tumours (no neoadjuvant treatment) (prevalent pool + any incident patients)	Diminishing population due to shift to neoadjuvant treatment (as supported by BCNA), particularly for this higher risk population

Compiled during PBAC evaluation using information from the pre-PBAC response, and p33 and p84 of the neratinib submission.
*71 of 740 patients in the T-DM1 arm switched to trastuzumab, 63 patients completed 14 cycles of HER-2 directed therapy (von Minckwitz et al (2019).

4.7 Therefore, the PBAC noted that, if T-DM1 is listed on the PBS, the relevant populations, in which there is clinical evidence for neratinib, would be limited to (i) patients with ≥T1cN0-3 tumours who do not receive neoadjuvant treatment and (ii) a prevalent pool of patients with residual disease following neoadjuvant treatment, who have been treated with adjuvant trastuzumab. The PBAC noted that both would be diminishing populations.

Figure 1: Clinical management algorithm of HER-2 positive breast cancer if neratinib (TDM-1 and pertuzumab) listed on the PBS (as presented in the submission)



Source: Figure 18, p60 of the resubmission

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

5 Comparator

5.1 The resubmission nominated usual care/placebo as the main comparator. This is unchanged from the original submission and the ESC noted this was considered reasonable by the PBAC previously (paragraph 5.1, neratinib PSD, March 2019).

5.2 The PBAC considered that 'both pertuzumab and T-DM1 could be considered near market comparators and the clinical place of neratinib would need to be considered with regard to potential changes in the clinical algorithm' (paragraph 7.5, neratinib PSD, March 2019).

5.3 The resubmission nominated pertuzumab in combination with trastuzumab and chemotherapy (Ptz+T+Chemo) as a near market comparator. The resubmission conducted an indirect comparison of neratinib (ExteNET trial) and pertuzumab (APHINITY trial), using trastuzumab plus chemotherapy (T+Chemo) as the common comparator.

5.4 The resubmission did not include T-DM1 as a near market comparator as per the PBAC recommendation (paragraph 5.2, neratinib PSD, March 2019). The resubmission stated that 'if in the future T-DM1 is registered and reimbursed in the adjuvant setting, it will be used as a substitute for trastuzumab in the adjuvant setting as follow-up therapy for a distinct pre-specified high risk neoadjuvant patient population who did not achieve a pathological complete response' (p47 of the resubmission).

5.5 The resubmission and Pre-Sub-Committee Response (PSCR) argued that the KATHERINE and ExteNET trials cannot be directly compared as the KATHERINE trial only included high-risk patients. The PSCR argued that T-DM1 should not be included as a near-market comparator because the patient population investigated in the KATHERINE study represented 10.5% of HR+ patients with <1 year from last dose of trastuzumab in the ExteNET study (Table 10 of the resubmission). The ESC noted that in the ExteNET study 17.2% of the ITT population initiated trastuzumab in the neoadjuvant setting and patients with prior neoadjuvant therapy were excluded if they achieved a pathologic complete response (pCR). As such, a substantial proportion of the ExteNET trial population overlapped with the KATHERINE trial population.

5.6 The resubmission also updated the proposed restriction to stop patients receiving sequential treatment with neratinib and T-DM1. If T-DM1 were to be listed on the PBS for HER2+ eBC, patients receiving T-DM1 would not be permitted to receive neratinib as a sequential treatment. However, patients unable to tolerate T-DM1 who switched to trastuzumab monotherapy would be permitted to receive neratinib as an extended adjuvant therapy following trastuzumab monotherapy.

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 sponsor addressed three key issues including the clinical place of therapy, the potential bias of the reconsenting process in the ExteNET trial, and the management of diarrhoea associated with neratinib. The PBAC considered that the information presented for the first two key issues did not add substantively to the evidence already presented in the submission. In relation to the management of diarrhoea as an adverse event, the sponsor highlighted that there are currently 280 patients in the patient access program and clinical data are currently being collected from this program. Dose escalation with neratinib was initiated in July 2019, which aligns with the dose management of haematology and oncology drugs. The sponsor noted that dose escalation together with the patient support program has helped patients and oncologists manage the adverse events associated with neratinib.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (37) and organisations (2) via the Consumer Comments facility on the PBS website. The PBAC noted the comments reported different levels of severity for the adverse effects associated with neratinib. The side effects included diarrhoea, tiredness and fatigue, dry skin, cramping, nose bleeds, brittle nails, lack of appetite and weight loss. In terms of diarrhoea, approximately three quarters of the comments reported minimal or manageable side effects (many described the side effects as initially difficult but then became manageable over the course of treatment). These comments noted that the side effects did not affect quality of life and that patients were able to work and exercise. A quarter of the comments described the side effects as major but noted it was better than chemotherapy. A number of comments noted that neratinib was discontinued due to the severity of diarrhoea. The comments also noted that there was more monitoring and testing required while on neratinib. Overall, the comments were supportive of neratinib, noting that despite the side effects, being able to prevent the return of cancer was a significant priority for patients and that more people would be prepared to tolerate the side effects for the first two months in order to gain greater benefit in the long term. The PBAC considered that the comments indicated that consumers were well-informed about managing the diarrhoea associated with neratinib.

6.3 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) clarifying the likely use of neratinib in clinical practice. The BCNA maintained its support for neratinib. The BCNA acknowledged the increasing use of neoadjuvant treatment in eBC however believed that there would be a patient population, albeit a small population, who would benefit from treatment with neratinib in the adjuvant setting following trastuzumab treatment. The BCNA also commented that each

eligible patient should have the right to decide whether, for them, the potential benefit outweighs the potential adverse events.

6.4 The Medical Oncology Group of Australia (MOGA) included neratinib in the category "other supported applications", on the basis of improved iDFS but noting that the OS benefit was immature. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for neratinib, and it was rated A (out of A, B and C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies)[2], based on a comparison with placebo.

Clinical trials

6.5 The resubmission was based on one head-to head randomised trial comparing neratinib to placebo: ExteNET (N=2840). This is unchanged from the original submission.

6.6 Table 4 presents the details of the trial presented in the resubmission.

Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
ExteNET (study 3004)	A Randomized Double-blind Placebo-Controlled Trial of Neratinib (HKI-272) After Trastuzumab in Women With Early-Stage HER-2/neu Overexpressed/Amplified Breast Cancer	April 2009
	Martin M; Holmes FA; Ejlertsen B et al. ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2+ breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial.	*Lancet Oncology* 2017; 18(12):1688-1700.
	Chan A; Delaloge S; Holmes FA et al ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2+ breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.	*Lancet Oncology* 2016, 17(3):367-77.
	Goss PE, Barrios CH, Chan A et al. A phase III trial of adjuvant neratinib (NER) after trastuzumab (TRAS) in women with early-stage HER2+ breast cancer (BC).	*Journal of clinical oncology*, 29(15 SUPPL. 1):, ASCO Annual Meeting 2011 Chicago, IL United States
	Ejlertsen B., Chan A., Gnant M et al. Timing of initiation of neratinib after completion of trastuzumab based adjuvant therapy in early-stage HER2+ breast cancer: Exploratory analyses from the phase III ExteNET trial.	San Antonio Breast Cancer Symposium, SABCS 2017. United States. 78 (4 Supplement 1) (no pagination), February 2018.
	Chia S.K.L., Martin M., Iwata H. et al. Effects of neratinib after trastuzumab-based adjuvant therapy in hormone receptor-positive HER2+ early-stage breast cancer: Exploratory analyses from the phase III ExteNET trial.	San Antonio Breast Cancer Symposium, SABCS 2017. United States. 78 (4 Supplement 1) (no pagination), February 2018.
	Chia S.K.L., Martin M., Holmes F.A. et al. PIK3CA alterations and benefit with neratinib after trastuzumab-based adjuvant therapy in	San Antonio Breast Cancer Symposium, SABCS 2017. United States. 78 (4 Supplement 1) (no

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

Trial ID	Protocol title/ Publication title	Publication citation
	early-stage HER2+ breast cancer: Correlative analyses of the phase III ExteNET trial.	pagination), 2018. Date of Publication: February 2018.
	Gnant M, Martin M, Holmes F-A, Jackisch C, Chia SK, Iwata H, et al. Efficacy of neratinib in hormone receptor-positive patients who initiated treatment within 1 year of completing trastuzumab-based adjuvant therapy in HER-2+ early-stage breast cancer: Subgroup analyses from the phase III ExteNET trial.	Presented at the San Antonio Breast Cancer Symposium; Dec 4-8, 2018. San Antonio, TX.
	Iwata H., Masuda N., Kim S.-B. et al. Neratinib in the extended adjuvant treatment of patients from Asia with early-stage HER2+ breast cancer after trastuzumab-based therapy: Exploratory analyses from the phase III ExteNET trial.	San Antonio Breast Cancer Symposium, SABCS 2017. United States. 78 (4 Supplement 1) (no pagination), 2018. Date of Publication: February 2018
	Martin Jimenez M., Holmes F.A., Ejlertsen B. et al. Neratinib after trastuzumab (T)-based adjuvant therapy in early-stage HER21 breast cancer (BC): 5-year analysis of the phase III ExteNET trial.	*Embase Classic+Embase Annals of Oncology* 42nd ESMO Congress, ESMO 2017. Spain. 28 (Supplement 5) (pp v43-v44), September 2017.
	Delaloge S., Ye Y., Cella D. et al. Effects of neratinib (N) on health-related quality of life (HRQoL) in early-stage HER21 breast cancer (BC): Longitudinal analyses from the phase III ExteNET trial.	42nd ESMO Congress, ESMO 2017. Spain. 28 (Supplement 5) (pp v53), September 2017.
	Mortimer J., Di Palma J., Jahanzeb M. et al. Characterization of neratinib-induced diarrhea in patients with early-stage HER2+ breast cancer: Analyses from the phase III ExteNET trial.	39th Annual CTRC-AACR San Antonio Breast Cancer Symposium. United States. 77 (4 Supplement 1) (no pagination), February 2017.
	Chan A., Delaloge S., Holmes F.A. et al. Neratinib after trastuzumab-based adjuvant therapy in early-stage HER2+ breast cancer: 3-year analysis from a phase 3 randomized, placebo-controlled, double-blind trial (ExteNET).	38th Annual CTRC-AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Publication: (var.pagings). 76 (4 SUPPL. 1) (no pagination), Feb 2016.
	Sudhan D.R., Schwarz L.J., Guerrero-Zotano A.L. et al. Extended adjuvant neratinib/fulvestrant blocks ER/HER2 crosstalk and maintains complete responses of ER+/HER2+ tumors following treatment with chemotherapy and anti-HER2 therapy.	San Antonio Breast Cancer Symposium, SABCS 2017. United States. 78 (4 Supplement 1) (no pagination), February 2018.
	Wang M., Tao Z. Safety and efficacy profile of neratinib in breast cancer: Pooled reanalysis based on randomized controlled trials.	Joint Meeting of the Multinational Association of Supportive Care in Cancer, MASCC and the International Society of Oral Oncology, ISOO 2018. Austria. 26 (2 Supplement 1) (pp S254-S255), 2018

Source: Table 26, p80 of the resubmission

6.7 The key features of the direct randomised trial are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Neratinib vs placebo						
ExteNET	2840	R, DB 60 months	Unclear	Initial protocol: HER2+, HR+ & HR-, lymph node positive & negative eBC; completed trastuzumab up to 2 years Amendment 3: HER2+, HR+ & HR-, lymph node positive eBC; completed trastuzumab up to 1 years	Primary outcome: iDFS of the ITT population, aITT population, Centrally-confirmed ERBB2-positive. Secondary outcome:DFS-DCIS, DDFS TTDR, Incidence of CNS recurrence; OS not available; FACT-B; EQ-5D	Unclear, but presumably iDFS in the HR+ population of the ITT analysis.

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; HER2+= human epidermal growth factor receptor 2 positive; HR+: hormone receptor positive; HR-: hormone receptor negative; eBC: early breast cancer; DFS-DCIS: DFS including ductal carcinoma in situ; DDFS: Distant disease-free survival; TTDR: Time to distant recurrence; CNS: Central Nervous System; FACT-B: Breast cancer-specific quality of life – FACT-B (version 4);
ITT: Intent to treat: The ITT population includes all randomised patients with the exceptions documented in the SAP. Patients were analysed by the randomised treatment arms regardless of the actual treatment received.
aITT: amended Intent to treat: The aITT population includes all patients randomised under global amendment 3 or later amendment, or all patients randomised prior to implementation of global amendment 3 if they met the following key criteria: 1. All patients with node-positive disease and 2. All patients randomised within 1 year from completion of prior trastuzumab therapy.
Centrally-confirmed ERBB2-positive: The Centrally Confirmed erbB-2-Positive population includes all patients randomised who were confirmed by central testing to be erbB-2 positive.
Source: compiled during the evaluation based on information provided in p40-43 of the resubmission

6.8 There were 14 protocol amendments throughout the five years of the ExteNET trial, of which six were global amendments.

6.9 Previously, the PBAC considered amendments 3, 9 and 13 contributed to an overall high risk of bias for the ExteNET trial (paragraph 7.6 neratinib PSD, March 2019). The resubmission attempted to address the PBAC concerns for each of these amendments. The PSCR noted that regardless of these amendments, all international regulatory and reimbursement agencies that have reviewed neratinib (NICE, EMA, Health Canada, TGA, FDA) have delivered positive recommendations on the basis of the HR+ subgroup analysis and none have concluded that the protocol amendments invalidated the results.

6.10 To address protocol amendments 9 & 13, which related to revising key statistical methods and follow-up periods, the resubmission stated that the Food and Drug Administration (FDA) conducted a tipping-point analysis, which showed that the missing survival data of the non-reconsented patients had a minimal impact on the trial results. The ESC agreed with the commentary that the tipping-point analysis did not take into consideration the disease recurrence rates in the patients not reconsented given this data was unknown. A comparison of the baseline characteristics of the reconsented patients compared with those not reconsented patients was not provided. Thus, the 5-year health outcome results may have favoured neratinib if the patients who were not reconsented had worse survival outcomes compared with the reconsented patients.

6.11 The ESC maintained its advice that the overall risk of bias for the ExteNET trial remained high.

6.12 The resubmission presented an indirect comparison of two trials: ExteNET (neratinib as an extended adjuvant therapy following trastuzumab plus chemotherapy (T+ Chemo)) and APHINITY (pertuzumab in combination with trastuzumab plus chemotherapy (Ptz+ T+ Chemo)). Trastuzumab plus chemotherapy (T+Chemo) was the common comparator. The March 2019 submission did not include this indirect comparison.

6.13 The key features of the trials included in the indirect comparison are summarised in Table 6.

Table 6: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Neratinib vs placebo					
ExteNET	2840	R, DB 60 months	high	Initial protocol: HER2+, HR+ & HR-, lymph node positive & negative eBC; completed trastuzumab up to 2 years Amendment 3: HER2+, HR+ & HR-, lymph node positive eBC; completed trastuzumab up to 1 years	Primary outcome: iDFS of the ITT population, aITT population, Centrally-confirmed ERBB2-positive. Secondary outcome:DFS-DCIS, DDFS TTDR, Incidence of CNS recurrence; OS not available; FACT-B; EQ-5D
Ptz+T+Chemo vs T + Chemo					
APHINITY	4,805	R, DB 45 mths	Low	HER2+ eBC	iDFS (primary outcome) OS, recurrence-free interval (RFI), distant RFI (DRFI), EORTC QLQ-C30 and EQ-5D-3L

DB=double blind; DRFI= distant recurrence free interval; EORTC=European organisation for research and treatment of cancer; iDFS=invasive disease-free survival; OS=overall survival; R=randomised; RFI=recurrence free interval; QLQ=quality of life questionnaire; Ptz=pertuzumab; T= trastuzumab; Chemo= chemotherapy; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; HER2+= human epidermal growth factor receptor 2 positive; HR+: hormone receptor positive; HR-: hormone receptor negative; eBC: early breast cancer; DFS-DCIS: DFS including ductal carcinoma in situ; DDFS: Distant disease-free survival; TTDR: Time to distant recurrence; CNS: Central Nervous System; FACT-B: Breast cancer-specific quality of life – FACT-B (version 4);
ITT: Intent to treat: The ITT population includes all randomised patients with the exceptions documented in the SAP. Patients were analysed by the randomised treatment arms regardless of the actual treatment received.; aITT: amended Intent to treat: The aITT population includes all patients randomised under global amendment 3 or later amendment, or all patients randomised prior to implementation of global amendment 3 if they met the following key criteria: 1. All patients with node-positive disease and 2. All patients randomised within 1 year from completion of prior trastuzumab therapy; Centrally-confirmed ERBB2-positive: The Centrally Confirmed erbB-2-Positive population includes all patients randomised who were confirmed by central testing to be erbB-2 positive.
Source: compiled during the evaluation based on neratinib PSD March 2019 meeting and pertuzumab March 2019 meeting

6.14 The ESC agreed with the commentary that the results of the indirect comparison should be interpreted with caution due to applicability and exchangeability issues due to differences between the two trials including trial design, timepoint of analysis, patient characteristics and the overall risk of bias. The ESC considered the indirect comparison was likely to favour neratinib. Given the ESC and PBAC considered that the indirect comparison was unreliable, the results have not been presented.

Comparative effectiveness

6.15 Table 7 presents the results of the iDFS for the ITT population, aITT population, and centrally-confirmed ERBB2 positive populations (i.e. HER+ population), and the sensitivity analyses of the iDFS for the ITT population. This is unchanged from the original submission.

Table 7: Results of iDFS of the ExteNET trial across the trials

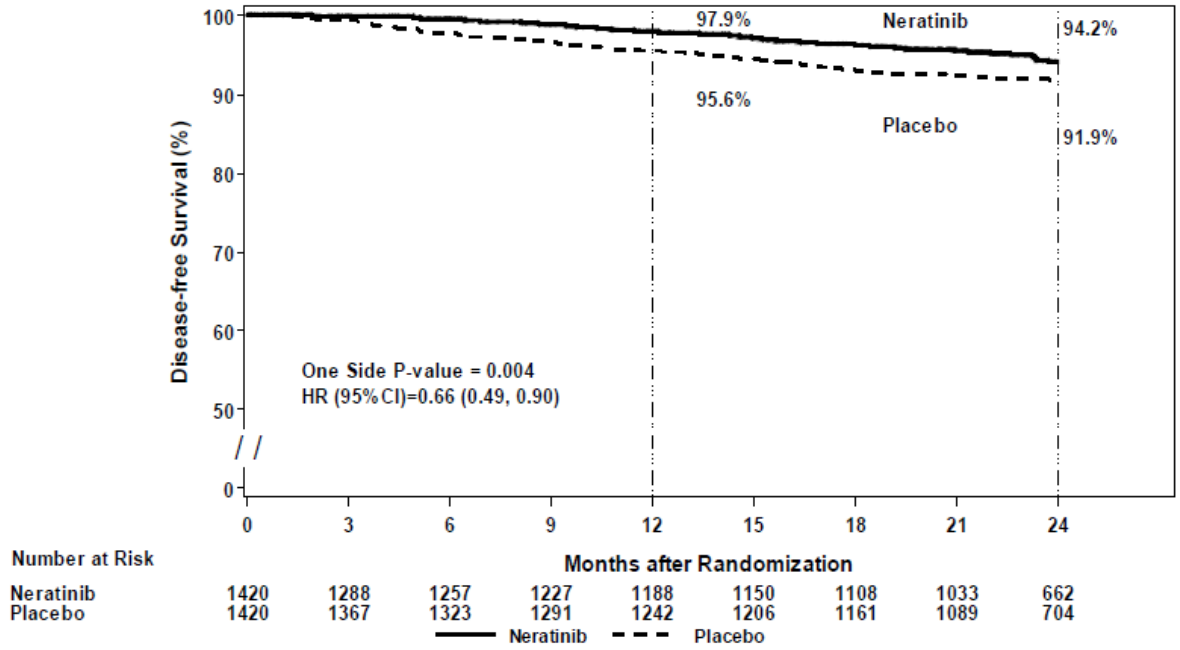
Population	Neratinib	Placebo	RD	P value (log rank test)	Hazard ratio (95% CI)
	n/N with event (%)	n/N with event (%)			
Primary analysis					
ITT (7 July 2014) (at 2 years)	Events: 67/1420 (4.7%) KM: 94.2 (92.6, 95.4)	Events: 106/1420 (7.5%) KM: 91.9 (90.2, 93.2)	2.3%	0.004	**0.66 (0.49, 0.90)**
ITT (1 March 2017) (at 2 years)	Events: 76/1420 (5.4%) KM: 94.3 (92.9, 95.4)	Events: 114/1420 (8.0%) KM: 91.7 (90.1, 93.1)	2.6%	0.004	**0.68 (0.51, 0.91)**
ITT (1 March 2017) (at 5 years)	Events: 116/1420 (8.2%) KM: 90.2 (88.3, 91.8)	Events: 163/1420 (11.5%) KM: 87.7 (85.7, 89.4)	2.5%	0.004	**0.73 (0.57, 0.92)**
aITT (7 July 2014) (at 2 years)	Events: 53/938 (5.7%) KM: 93.1 (91.1,94.7)	Events: 84/935 (9.0%) KM: 90.1 (87.9,92.0)	3.0%	0.007	**0.65 (0.46, 0.92)**
Centrally confirmed ERBB2-positive (7 July 2014) (2 year follow-up)	Events: 32/741 (4.3%) KM: 94.9 (92.8,96.3)	Events: 61/722 (8.4%) KM: 90.9 (88.5,92.9)	4.0%	<0.001	**0.51 (0.33,0.78)**
Sensitivity analyses of ITT					
Effect of Censoring (Site Early Dropout Rate <10%) (7 July 2014) (at 2 years)	Events: 57/1420 (4.0%) KM: 94.1 (92.4,95.4)	Events: 88/1420 (6.2%) KM: 91.6 (89.7,93.1)	2.5%	0.008	**0.66 (0.47, 0.93)**
Effect of Censoring (Site Completed Follow-up ≥90%)(7 July 2014) (at 2 years)	Events: 43/1420 (3.0%) KM: 93.9 (91.8,95.4)	Events: 67/1420 (4.7%) KM: 91.3 (89.1,93.1)	2.6%	0.028	0.69 (0.47, 1.01)

CI: confidence interval; DFS-DCIS: disease free survival including ductal carcinoma in situ; DDFS: Distant disease-free survival; FACT-B: Breast cancer-specific quality of life – FACT-B (version 4); iDFS: invasive disease free survival; KM: Kaplan-Meier; NA: not available; RD: risk difference; TTDR: Time to distant recurrence. ITT: Intent to treat: The ITT population includes all randomised patients with the exceptions documented in the SAP. Patients were analysed by the randomised treatment arms regardless of the actual treatment received
aITT: amended Intent to treat: The aITT population includes all patients randomised under global amendment 3 or later amendment, or all patients randomised prior to implementation of global amendment 3 if they met the following key criteria: 1. All patients with node-positive disease and 2. All patients randomised within 1 year from completion of prior trastuzumab therapy. Centrally confirmed ERBB2-positive: The Centrally Confirmed erbB-2-Positive population includes all patients randomised who were confirmed by central testing to be erbB-2 positive.
Bold indicates statistically significant results at the 5% level.
Source: compiled during the evaluation based on information provided in Table37, p110 of the resubmission; p117-118 of the CSR (Clinical Study Report).

6.16 For the ITT population, iDFS at 2 years (7 July 2014 analysis) was 94.2% with neratinib and 91.9% with placebo. The HR for iDFS was statistically significant (HR=0.66, 95% CI: 0.49, 0.90, P=0.004) but the absolute benefit in terms of the difference in iDFS was small (2.3% at 2 years). In terms of the ESMO MCBS, this would equate to a Grade A clinical benefit. However, this may fall to Grade C with the availability of OS data if the absolute difference in OS is like iDFS.

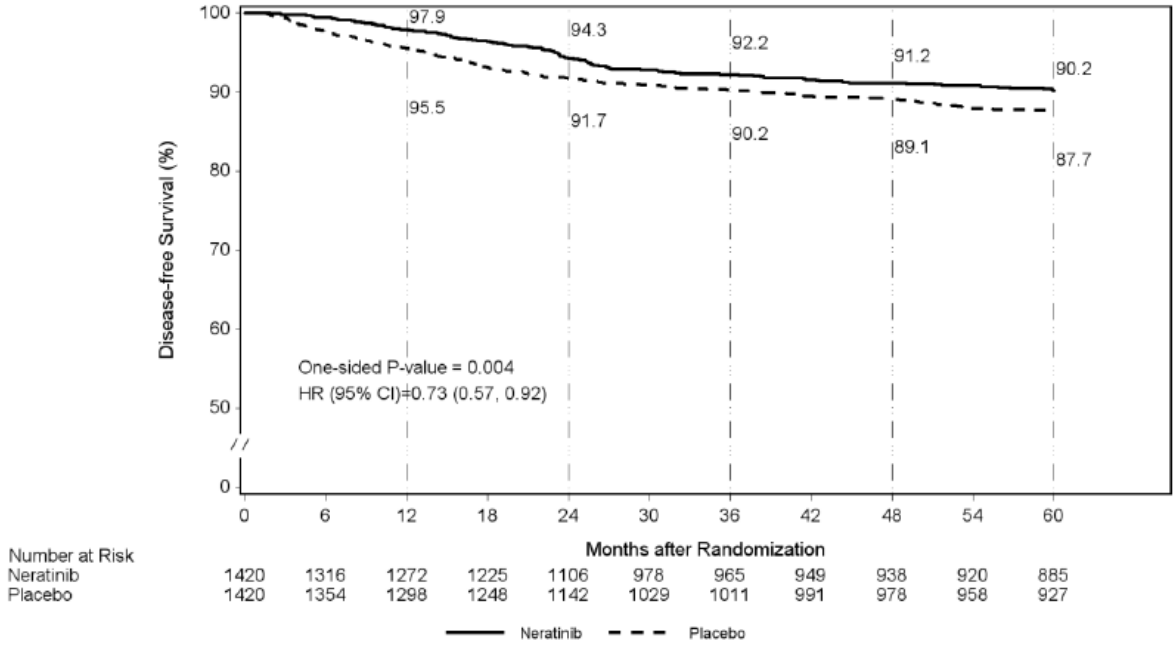
6.17 Figure 2 shows the Kaplan-Meier plot of the iDFS analyses for the ITT population on 7 July 2014 and Figure 3 shows the Kaplan-Meier plot of the iDFS analyses for the ITT population on 1 March 2017, following re-consenting of patients (and thus high levels of censoring). The 2-year iDFS results from both time points were similar.

Figure 2: Kaplan-Meier Plot of Disease free survival-ITT population (July 2014 analysis)



Source: Figure 21, p110 of the resubmission

Figure 3: Kaplan-Meier Plot of 5-year Disease-free Survival (All Data for Censoring), ITT Population (March 2017 analysis)



Source: Figure 22, p111 of the resubmission

6.18 The HR for iDFS based on the 1 March 2017 analysis was less favourable (closer to 1) than for the 7 July 2014 analysis but still statistically significant (HR=0.73, 95% CI: 0.57, 0.92, p=0.004 as reported in the CSR and p=0.0083 as reported in Martin et al. 2017). The absolute benefit in terms of the difference iDFS at 5 years remained small (2.5%).

6.19 The ESC previously questioned 'the clinical meaningfulness of the iDFS benefit given no OS data were available. Although the 2 year follow up data showed a significant improvement in iDFS, the ESC considered the difference to be small in absolute terms, and uncertain given the risk of bias and concerns regarding the applicability of the trial evidence to the PBS population' (paragraph 6.37, neratinib PSD, March 2019). The ESC noted that no additional OS data were available and maintained the view that the clinical meaningfulness of the iDFS benefit is unclear.

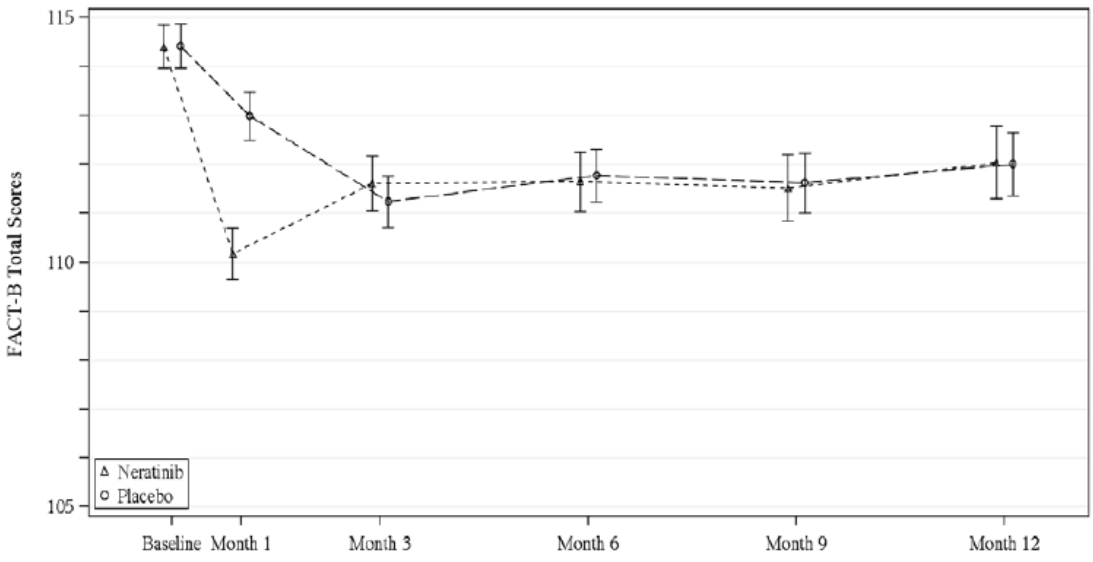
6.20 The resubmission argued that 'after 5 years of follow-up, extended adjuvant neratinib significantly reduced the risk of clinically significant relapse with no increased risk of long-term toxicities. The absolute benefit in the ITT population was 2.5% (HR 0.49; 95% CI 0.30–0.78; p=0.002) and the absolute benefit in HR positive cohort ≤1 year from trastuzumab was 5.1% (HR 0.58; 95% CI 0.41–0.82; p=0.002)' (p3 of the resubmission). The ESC noted that these 5 year outcomes were impacted by re-consenting issues discussed above.

6.21 Overall survival (OS) data was not presented. The PBAC considered that any resubmission would need to provide available OS data (paragraph 7.17, neratinib PSD, March 2019). The resubmission stated that the OS data will not be available until the

first half of 2020 and the OS data for patients with HR+ disease will not be available until 2024-2027.

6.22 The average FACT-B total score over time is shown in Figure 4 and the average EQ-5D Health State over time is shown graphically in Figure 5.

Figure 4: Average FACT-B Total Scores Over Time, ITT Population

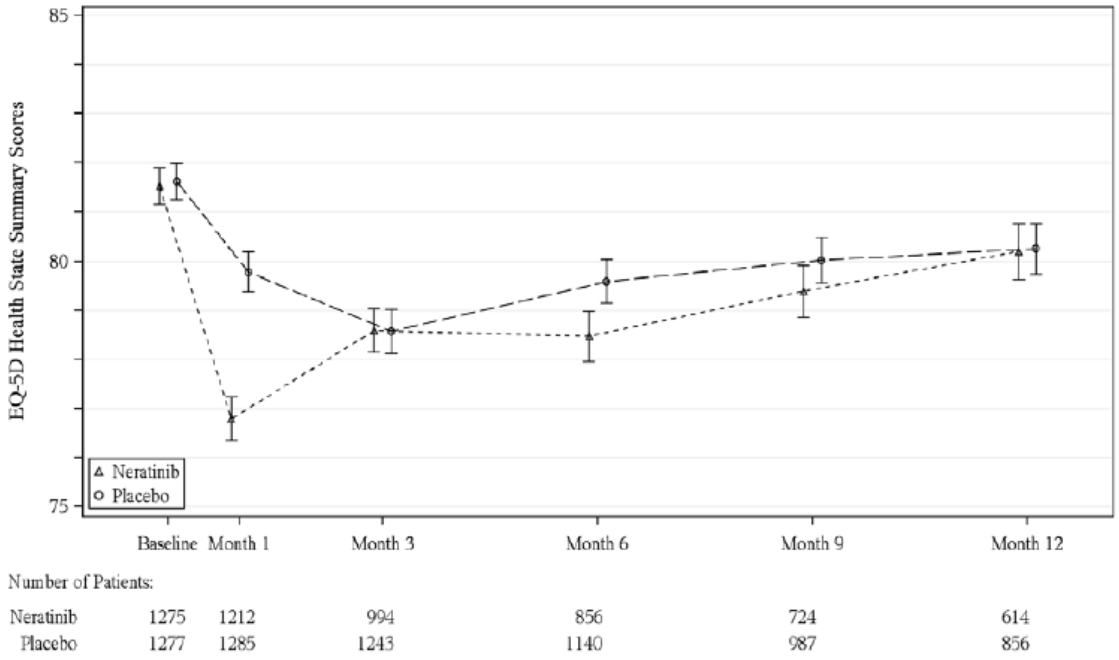


Number of Patients:

Neratinib	1264	1201	987	853	716	611
Placebo	1273	1274	1236	1135	978	853

Source: Figure 8, p119 of the resubmission

Figure 5: Average EQ-5D Health State Summary Scores Over Time, ITT Population



Source: Figure 8, p120 of the resubmission

6.23 The health-related quality of life pattern derived from the EQ-5D instrument was similar compared with using the FACT-B instrument. The quality of life results suggested within the first month after randomisation, the quality of life score decreased more with neratinib than with placebo. This may be due to the onset of diarrhoea. After the first month, the quality of life scores were similar for the two arms. However, the results suggested that neratinib does not significantly improve health-related quality of life.

6.24 Table 8 presents the key subgroup analyses results of the ExteNET trial. This is unchanged from the original submission.

Table 8: iDFS results for subgroups based on HR status (7 July 2014 analysis)

Population	Neratinib n/N (%)	Placebo n/N (%)	Neratinib 24-month iDFS rate, % (95% CI)	Placebo 24-month iDFS rate, % (95% CI)	P value (log rank test)	Hazard ratio (95% CI)
ITT	67/1,420 (4.7%)	106/1,420 (7.5%)	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)	0.004	**0.66 (0.49, 0.90)**
HR+	29/816 (3.6%)	63/815 (7.7%)	95.6 (93.8, 96.9)	91.5 (89.2, 93.3)	<0.001	**0.49 (0.31, 0.75)**
HR-	38/604 (6.3%)	43/605 (7.1%)	92.2 (89.4, 94.3)	92.4 (89.8, 94.3)	0.365	0.93 (0.60, 1.43)

CI: confidence interval; n: number of participants reporting data; N: total participants in group; ITT: intent to treat; iDFS; iDFS: invasive disease free survival; HR+: hormone receptor positive; HR-: hormone receptor negative.
Bold indicates statistically significant at the 5% level.
Source: compiled during the evaluation, based on Table 19, p121 of the CSR

6.25 Results from the pre-specified subgroup analysis by HR status showed that the improvement in iDFS was greater among patients with HR+ disease (2-year iDFS rate: neratinib arm=95.6%, placebo arm=91.5%, HR=0.49, P<0.001) compared with patients with HR- disease (2-year iDFS rate: neratinib arm=92.2%, placebo arm= 92.4%, HR=0.93, P=0.365). The results indicated that the clinical outcomes were significantly improved for HR+ patients compared to HR- patients.

Comparative harms

6.26 Table 9 presents a summary of patient-relevant harms, based on the ExteNET trial. This is unchanged from the original submission.

Table 9: Summary of key adverse events in ExteNET trial

Trial ID	Neratinib n with event/N (%)	Placebo n with event/N (%)	RR (95% CI)*
Any TEAE – n (%)	1387/ 1408 (98.5)	1240/ 1408 (88.1)	**1.119 (1.096, 1.141)**
Grade 3 or 4 TEAE	700/ 1408 (49.7)	184/ 1408 (13.1)	**3.804 (3.292, 4.396)**
Fatal TEAE	2/ 1408 (0.1)	1/ 1408 (0.1)	2.000 (0.182, 22.032)
Serious TEAE (SAE)	103/ 1408 (7.3)	85/ 1408 (6.0)	1.212 (0.918, 1.599)
Treatment-related TEAE	1353/ 1408 (96.1)	805/ 1408 (57.2)	**1.681 (1.605, 1.761)**
Serious Treatment-related TEAE	42/ 1408 (3.0)	8/ 1408 (0.6)	**5.250 (2.474, 11.142)**
TEAE Leading to Treatment Discontinuation	388/ 1408 (27.6)	76/ 1408 (5.4)	**5.105 (4.038, 6.454)**
TEAE Leading to Study Withdrawal	32/ 1408 (2.3)	7/ 1408 (0.5)	**4.571 (2.025, 10.322)**
TEAE Leading to Dose Reduction	440/ 1408 (31.3)	35/ 1408 (2.5)	**12.571 (8.982, 17.595)**
TEAE Leading to Hospitalisation	93/ 1408 (6.6)	75/ 1408 (5.3)	1.240 (0.558, 0.796)
TEAE Leading to Dose Hold	629/ 1408 (44.7)	187/ 1408 (13.3)	**3.364 (2.908, 3.891)**

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; SAE: Serious Treatment-emergent adverse events; TEAE: Treatment-emergent adverse events
Bold indicates statistically significant at the 5% level.
*Values were estimated during the evaluation
Source: Table 45, p125 of the resubmission

6.27 The ESC previously noted that 'the AE data show a clear pattern of increased risk of serious treatment related TEAE, including those leading to withdrawal/dose reduction. The toxicity level of neratinib was high, especially in terms of diarrhoea' (paragraph 6.32, neratinib PSD, March 2019).

6.28 The ESC also previously noted the ExteNET trial excluded patients with significant gastroenterological conditions with a primary symptom of diarrhoea, including any Grade ≥2 diarrhoea. Although diarrhoea is an adverse event for other treatments used in eBC, such as pertuzumab and trastuzumab, the ESC considered that the severe diarrhoea experienced by patients treated with neratinib trial will impact on the attrition levels in clinical practice and therefore on treatment effectiveness (paragraph 6.32, neratinib PSD, March 2019).

6.29 The PBAC previously noted that 'for patients treated with neratinib 30% had a dose reduction, 44% had a dose hold and 27% discontinued treatment' and considered that

'there would be some reduction in diarrhoea with loperamide prophylaxis, however neratinib would remain a difficult drug to manage in practice due to its toxicity' (paragraph 6.32, neratinib PSD, March 2019).

6.30 Diarrhoea was a common adverse event for patients with eBC who were treated with pertuzumab, trastuzumab or neratinib. However, more patients treated with neratinib experienced grade 3 or 4 diarrhoea in the ExteNET trial compared with patients treated with Ptz+T+Chemo in the APHINITY trial. The relative risk was statistically significant (RR=9.319, CI: 4.498, 19.310) and the odds ratio was also statistically significant (OR=14.292, CI: 8.722, 23.419). The PSCR argued that the multiple cohort CONTROL study demonstrated that the use of prophylactic loperamide reduced the incidence, duration, and severity of diarrhoea. The ESC noted the CONTROL trial was presented in the previous consideration and maintained the view that the results of the CONTROL trial should be interpreted with caution as the risk of bias may be high due to it being an open label trial. The ESC noted that loperamide was not allowed in the ExteNET trial and considered that in clinical practice, loperamide may not be sufficient to manage the severity of grade 3 or 4 diarrhoea. The PBAC noted in the consumer comments that prophylactic anti-diarrhoeal medication, together with dose escalation within the current patient access program has helped to manage the adverse events associated with neratinib.

Benefits/harms

6.31 A summary of the comparative benefits and harms for neratinib versus placebo is presented in Table 10. This is unchanged from the March 2019 submission.

Table 10: Summary of comparative benefits and harms for neratinib and placebo

iDFS at 2 years (7 July 2014) (at 2 years)				
	Neratinib	**Placebo**	**Absolute difference**	**HR (95% CI)**
iDFS (ITT population)				
iDFS, % (95% CI)	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)	2.3%	0.66 (0.49,0.90)
Median iDFS (months)	NA	NA	NA	
iDFS (aITT)				
iDFS, % (95% CI)	93.1 (91.1,94.7)	90.1 (87.9,92.0)	3.0%	0.65 (0.46, 0.92)
Median iDFS (months)	NA	NA	NA	
iDFS (Centrally confirmed ERBB2-positive)				
iDFS, % (95% CI)	94.9 (92.8,96.3)	90.9 (88.5,92.9)	4.0%	0.51 (0.33,0.78)
Median iDFS (months)	NA	NA	NA	
iDFS (HR+)				
iDFS, % (95% CI)	95.6 (93.8,96.9)	91.5 (89.2,93.3)	4.1%	0.49 (0.31,0.75)
Median (months)	NA	NA	NA	

Harms						
	Neratinib n/N (%)	**Placebo n/N (%)**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				Neratinib	**Placebo**	
Grade ≥3 TEAE	700/1408 (49.7)	184/1408 (13.1)	3.804 (3.292,4.396)	49.7	13.1	36.6% (33.5%, 39.8%)
SAE	103/1408 (7.3)	85/1408 (6.0)	1.212 (0.918, 1.599)	7.3	6.0	1.3% (-0.6%, 3.1%)
Any grade diarrhoea	1343/1408 (95.4)	499/1408 (35.4)	2.691 (2.506, 2.891)	95.4	35.4	59.9% (57.2%, 62.7%)
Any Grade 3 or 4 diarrhoea	562 /408 (39.9)	23/1408 (1.6)	24.435 (16.210, 36.832)	39.9	1.6	38.3% (35.6%, 40.9%)

CI = confidence interval; n = number of participants reporting data; N = total participants in group; NR: not relevant; iDFS: invasive disease-free survival; HR+: hormonal receptor positive; HR-: hormonal receptor negative; HR: relative risk;
Source: Compiled during the evaluation. Table 19, p121 of the CSR; based on Table 19, p121 of the CSR; Figure 34, p137 of the resubmission; Table 45, p125 of the resubmission; Table 46, p126 of the submission; Table 47, p127 of the resubmission

6.32 On the basis of the direct evidence presented by the resubmission, for every 100 patients treated with neratinib in comparison to placebo and follow-up of 24 months:

- Approximately 2-4 additional patients would not experience recurrence.
- Approximately 4 additional HR+ patients would not experience recurrence.
- Approximately 37 additional patients would experience a grade ≥3 TEAE.
- Approximately 1 additional patient would experience a SAE.
- Approximately 60 additional patients would experience diarrhoea.
- Approximately 38 additional patients would experience grade 3 or 4 diarrhoea

Clinical claim

6.33 The resubmission described neratinib as superior in terms of effectiveness compared with placebo in patients with HER2+ eBC. The resubmission also described neratinib as inferior in terms of safety compared to placebo. This is unchanged from the original submission.

6.34 However, the PBAC previously considered that 'the magnitude of the disease free survival benefit is small and uncertain due to potential bias in the ExteNET trial and because the study was not powered to detect effects within subgroups. The PBAC noted that the clinical benefit was particularly uncertain in lower risk populations such as stage 1 and node negative patients. The PBAC noted the lack of overall survival data in the evidence presented, and thus the long term benefits of neratinib therapy are unknown' (paragraph 6.39, neratinib PSD, March 2019).

6.35 The PSCR argued that the EMA EPAR states "Nerlynx had been shown to be of benefit in women with HER2-positive early breast cancer, and that this benefit seemed to be mainly in women with hormone-receptor positive disease" (EPAR). Further the NICE appraisal committee concluded that the ExteNET study was "suitable for estimating the clinical effectiveness of neratinib" in the subgroup of patients with hormone receptor positive disease who have received trastuzumab therapy within 12 months. The ESC maintained its view from its previous consideration that the clinical meaningfulness of the iDFS benefit was questionable given the absence of OS data. Although the 2 year follow up data showed a statistically significant improvement in iDFS, the ESC considered the difference to be small in absolute terms, and uncertain given the risk of bias and concerns regarding the applicability of the trial evidence to the PBS population, which was still unclear.

6.36 The proposed place for neratinib in the clinical management algorithm excluded higher risk patients (with residual disease after neoadjuvant therapy), who would be treated with T-DM1 if PBS listed. The ESC agreed with the commentary that the exclusion of higher risk patients from the likely treatment population is likely to mean that the clinical benefit in practice is less than that shown in the trial.

6.37 The PBAC previously considered that 'the claim of inferior comparative safety was reasonable and consistent with the data. The adverse events experienced with neratinib therapy compared to placebo were significant and may outweigh the benefit for some patients' (paragraph 6.40, neratinib PSD, March 2019). The ESC noted that no additional evidence was provided and reiterated its view from its previous consideration that for patients who have undergone a substantial amount of previous treatment for their cancer, a significant proportion would be unwilling to undertake further treatment that is associated with diarrhoea that may result in hospitalisation (paragraph 6.35, neratinib PSD, March 2019).

6.38 The resubmission also stated that neratinib was more effective than pertuzumab in HR+ patients (HR: 0.576, 95% CI: 0.31, 0.75). This claim was based on an indirect comparison of neratinib (ExteNET trial) and pertuzumab (APHINITY trial), with T+Chemo as the common comparator. The HR of the comparative treatment effect was statistically significant for the HR+ subgroup but not statistically significant for the ITT population or the aITT population. The ESC considered that this comparison was unreliable because of the applicability and exchangeability issues across the two trials.

6.39 The PBAC maintained its view from its previous consideration that the magnitude of the disease free survival benefit is small and uncertain due to potential bias in the ExteNET trial and because the study was not powered to detect effects within subgroups. The PBAC noted that the clinical benefit was particularly uncertain in lower risk populations such as stage 1 and node negative patients. The PBAC noted the lack of overall survival data in the evidence presented, and thus the long term benefits of neratinib therapy are unknown.

6.40 The PBAC maintained its view that the claim of inferior comparative safety of neratinib over placebo was reasonable and consistent with the data.

Economic analysis

6.41 The resubmission presented a cost-utility and cost-effectiveness analysis comparing neratinib to usual care/placebo, based on the ExteNET trial, Australian mortality data and data from published literature. The resubmission implemented a modelled evaluation. The resubmission did not present a stepped economic evaluation. This approach is unchanged from the original submission however the model structure, time horizon and input data sources have changed. Although the documentation provided with the model was improved from the original submission and some of the PBAC's previous concerns were addressed, not all issues were addressed by the resubmission. The ESC considered that the changes to the model structure, assumptions and inputs introduced additional uncertainty to the economic evaluation. Overall, the ESC considered the economic base case presented in the resubmission was highly optimistic due to assumptions and inputs that favoured neratinib and was highly uncertain given the lack of clarity around the clinical place and target population.

6.42 The resubmission outlined a changed proposed clinical management algorithm compared to the original submission. This was not reflected in the economic model which does not exclude higher risk patients who were included in the ExteNET trial. Excluding higher risk patients from the economic evaluation would likely reduce the incremental benefit of neratinib. The ESC advised that the model needed to accurately reflect the requested patient population and appropriate treatment effect (i.e. a lower risk population if T-DM1 is preferentially used to treat higher risk patients). The ESC considered that having a clear place in therapy was fundamental to the evaluation of the cost-effectiveness of neratinib.

6.43 Table 11 summarises the key outstanding matters of concern for the economic evaluation in the original submission and how these have been addressed.

Table 11: Summary of model issues in identified

Component	Matter of concern	How the resubmission addresses it
Modelled OS data	The model incorporated a substantial gain in OS despite no OS data from the ExteNET trial being presented in the submission (para 6.47, 7.15, 7.17).	No OS data are presented in the resubmission or economic evaluation. The economic model uses Australian general population mortality and PDRS to model survival. The ESC considered the resubmission did not adequately address this issue.
Data sources used to inform transition probabilities	Three separate data sources (ExteNET trial, HERA trial, and UK general population data) informed iDFS and OS (para 6.48).	Two data sources (ExteNET and Australian general population data) inform iDFS and OS. The model structure was changed to include a fifth health state (remission) with two new transitions estimated from external sources. This attempted to address PBAC's concern, however OS data from the ExteNET trial would be preferable.
Extrapolation of iDFS	The ESC considered that using observed data would likely result in an increased ICER but this was difficult to quantify (para 6.49). The base case applied a Gompertz function to extrapolate the data despite the AIC and BIC results suggesting there were better fitting functions (para 6.51)	No observed data from the ExteNET trial is included in the economic evaluation. The ESC noted that the resubmission did not address this concern. The base case applied a flexible spline Weibull (1 knot) function for iDFS which was the best statistical fit. This addressed ESC's concern, however the ICER is highly sensitive to the iDFS extrapolation function.
Duration of treatment effect	The iDFS and OS treatment effect tapered to a HR of 1 between 5.25 years and 15.25 years. The ESC considered the duration of treatment effect is highly uncertain (para 6.50).	The iDFS treatment effect is tapered to a HR of 1 between 5.25 years and 13.9 years. PDRS uses blinded data, no tapering is applied. This attempted to address the ESC's concern; however, the duration of treatment effect is justified using a different patient population to the rest of the economic model and is therefore uncertain.
Utility values	The submission applied utility estimates from the literature rather than applying the utility estimates from the ExteNET trial for the iDFS health state (para 6.52, 6.60). Utility estimates for locoregional recurrence and distant recurrence health states were identical (para 6.53). Disutilities were only applied for diarrhoea, and the duration they were applied for was shorter for neratinib than for placebo for Grade ≤ 2 diarrhoea (para 6.54).	ExteNET data is applied for the iDFS and remission health states. Trial data was not provided and could not be verified. The ESC noted there is a substantial amount of missing data in both treatment arms of ExteNET as patients who discontinue treatment are not included. This may overestimate the utility values, favouring neratinib. Different utilities were applied to locoregional recurrence and distant. This attempts to address PBAC's concern however there are issues with the accuracy of the estimates applied from the literature and bias in the sources used which may overestimate utility values, favouring neratinib. Disutilities were applied for all frequently reported AE ≥ grade 3. Duration of disutility was drawn from ExteNET. This addressed PBAC's concern.
Neratinib cost	The model calculated the drug cost by multiplying the monthly cost by the proportion disease free for the duration of 8.23 months, however the mean duration (of 8.23) already accounted for discontinuation of patients who have progressed.	The resubmission used the mean duration of 8.1 months (based on the HR+ population who received neratinib within 12 months of trastuzumab) rather than 8.23 (ITT population) but did not address this issue or include wastage, which underestimated the costs.

	Wastage was not included in the base case (para 6.56 & 7.15).	
Health care resource costs	The use of loperamide was underestimated, cost of endocrine therapies were not included, several medical service/diagnostic costs were not included, several treatments for adverse events and subsequent therapy following disease recurrence were inappropriate (para 6.55 & 7.15).	Use of loperamide is less than original submission and therefore this issue was not addressed. Endocrine therapy and additional medical service/diagnostic costs are included. This addressed PBAC's concern. Adverse event treatments and subsequent therapies are updated. This attempted to address PBAC's concern however some subsequent therapies in the resubmission are inappropriate as they are not consistent with existing PBS listings. The duration of subsequent treatment following recurrence is likely overestimated, favouring neratinib.
Age of modelled cohort	The age of the cohort in the model was derived from the mean age in the ExteNET trial rather than the mean age of newly diagnosed breast cancer patients in Australia (para 6.55).	The age in the resubmission (51.2 years) is younger than in the original submission (52.3). The resubmission proposed that this difference is justified as HR+ patients tend to be younger. This justification is uncertain. The PSCR argued that the mean age in the modelled population is consistent with the average age in the three most recent clinical trials in eBC and the Australian patients in the NAP. However, the ESC noted that the mean/median age of NAP and the clinical trial patients is consistently below that observed for women with eBC in Australia and therefore not representative of the specific women to whom the requested listing would apply.

AE: adverse event, eBC: early breast cancer, HR: hormone receptor, iDFS: invasive disease free survival, LR: locoregional recurrence, mBC: metastatic breast cancer, NAP: Nerlynx Access Program, OS: overall survival, PDRS: post distant recurrence survival, PSCR: pre-sub-committee response, Ptz: pertuzumab, T: trastuzumab, T-DM1: trastuzumab emtansine.
Source: Neratinib Public Summary Document (PSD), March 2019, Neratinib resubmission for November 2019 PBAC meeting, Table 14, p47 of the resubmission, Table 23, p72 of the resubmission.

6.44 Table 12 presents the key drivers of the economic model.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Extrapolation function	Base case uses flexible-spline Weibull (1 knot) to extrapolate iDFS for the duration of the trial. Choice of extrapolation function was identified as a driver of uncertainty in the original submission as only selected functions could be tested in the model.	High, favours neratinib ICER $[redacted] with generalised gamma function
Dosage/wastage	210 mg daily for 8.1 months (7.10 prescriptions) rather than 8.58 prescriptions used to estimate the financial impact. The dosage in the resubmission has changed from the original submission and continues to drive the ICER.	High, favours neratinib ICER $[redacted] with 12 month treatment duration (vs 8.1 months); $[redacted] with wastage
Subsequent treatment	The duration of subsequent treatment is based on a UK submission for pertuzumab in eBC (NICE TA569) which assumes treatment durations longer than the 2018 DUSC analysis of medicines for the treatment of HER2+ metastatic breast cancer. The duration of treatment in the modelled population is uncertain and likely overestimated.	High, favours neratinib ICER $[redacted]- $[redacted] with DUSC duration; ICER $[redacted] with DUSC duration and 12 month treatment duration
Treatment effect	Treatment effect continued beyond 5 year ExteNET follow-up period, tapering to a HR=1 13.9 years post follow-up	Moderate, favours neratinib ICER $[redacted] tapered to 10.2 yrs
Overall survival	No overall survival data were presented in the resubmission. The PBAC identified that incorporating a substantial gain in OS despite no OS data from the ExteNET trial was an assumption that was uncertain and likely to favour neratinib (para 7.15, neratinib PSD, March 2019)	Uncertain, likely to favour neratinib
Extrapolation data sources	Transition probabilities were based on fitted extrapolation functions for the entirety of the model. Kaplan Meier data were not included in the model so the visual fit of extrapolated functions could not be verified. This is unchanged from the original submission.	Uncertain
Cohort age	The mean age of the modelled population is 51.2 years, compared with 58.5 years reported in a 2004 study of Australian women with eBC[3]. Cohort age was identified as an applicability issue in the original submission. The age of patients in the model is younger than the original submission (52.3 years).	Uncertain, a coding error in the model meant the impact of this uncertainty could not be assessed during the evaluation. The PSCR stated that adjusting the patient age to 58.5 years resulted in an ICER of $[redacted]/QALY, however this could not be verified.

ICER: incremental cost effectiveness ratio
Source: Compiled during the evaluation

6.45 Table 13 shows the results of the economic evaluation presented in the March 2019 original submission and November 2019 resubmission.

[3] Davis et al (2004). Assessing the Support Needs of Women with Early Breast Cancer in Australia. Cancer Nursing. 27(2) (pp169-174).

Table 13: Results of the economic evaluation

Component	Neratinib	Placebo	Increment
Original submission			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
LYs	14.66	13.89	0.78
QALYs	12.84	12.14	0.70
Incremental cost/extra QALY gained – March 2019 submission			$ [redacted]
Resubmission			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
LYs	15.19	14.59	0.59
QALYs	12.56	12.02	0.55
Incremental cost/extra QALY gained – November 2019 resubmission			$ [redacted]

ICER: incremental cost-effectiveness ratio, LYs: life years, QALYs: quality adjusted life years
Source: Neratinib Ratified Public Summary Document, March 2019, Table 11, p27; Table 96, p222 of the resubmission.

6.46 The ESC considered the results presented by the resubmission remain uncertain given the lack of OS data, and model issues identified above.

6.47 The number of recurrence events over the 63-month trial follow-up period and 40-year model time horizon are compared in Table 14. Over the 40-year time horizon each patient treated with neratinib gained 1.59 life years. There were 5 (1.59/0.30 per patient) life years gained per distant recurrence avoided.

Table 14 Disaggregated summary of health outcomes (patients with distant and local recurrence) included in the economic evaluation

Outcome	Neratinib	Placebo	Incremental outcome (per patient)
LY (40 years, undiscounted)	**30.17**	**28.58**	**1.59**
Distant recurrence			
Trial distant recurrence (63 months)[a]	0.15	0.23	-0.08
Model distant recurrence (40 years)[a]	0.56	0.86	-0.30
Local recurrence			
Trial local recurrence (63 months)[b]	0.01	0.04	-0.03
Model local recurrence (40 years)[b]	0.03	0.09	-0.05

LY= life years.
a sum of columns AU and AV in sheets Markov-Int and Markov-Comp of Nerlynx_PBAC_Section3_July2019 workbook up to 63 months (trial) and 40 years
b sum of column AS in sheets Markov-Int and Markov-Comp of Nerlynx_PBAC_Section3_July2019 workbook up to 63 months (trial) and 40 years

6.48 The resubmission performed univariate scenario analyses. Results are summarised in Table 15. The resubmission claimed that the ICER was most sensitive to the duration of treatment effect and duration of metastatic treatment. Additional scenario analyses performed during the evaluation indicate that the ICER was most sensitive to the extrapolation of iDFS and the duration of treatment with neratinib.

Table 15: Results of scenario analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	**$**	**0.55**	**$**
Extrapolation iDFS (base case flexible spline Weibull, 1 knot)			
Gompertz extrapolation	$	0.55	$
Generalised gamma extrapolation	$	0.33	$
Incorporate HERA data with flexible spline Weibull, 2 knots	$	0.55	$
Treatment effect (base case waning to no effect at 13.9 years)			
Treatment effect continues to time horizon	$	0.68	$
Treatment effect wanes to no effect at 10.2 years	$	0.50	$
Assume no treatment effect after end of trial follow-up	$	0.41	$
Health state utilities (base case ExteNET, Lidgren 2007 and Lloyd 2006)			
Lidgren 2007	$	0.47	$
Treatment duration – P+T+D and T-DM1 for mBC (base case NICE TA569)			
DUSC Analysis (median length of treatment, excl. breaks)	$	0.55	$
DUSC Analysis (median number of scripts per patient)	$	0.55	$
Australian PI (median time to progression for P+T+D, T-DM1, T+D, and L+C)	$	0.55	$
Treatment duration – neratinib (base case 8.1 months)			
12 months	$	0.55	$
Wastage – neratinib (base case cost per tablet)			
Cost per pack	$	0.55	$
Time horizon (base case 40 years)			
10 years	$	0.12	$
20 years	$	0.34	$
30 years	$	0.48	$
35 years	$	0.52	$
45 years	$	0.55	$
50 years	$	0.56	$
Multivariate analyses			
Treatment duration – neratinib (base case 8.1 months) 12 months AND Treatment duration – P+T+D and T-DM1 for mBC (base case NICE TA569) DUSC Analysis (median length of treatment, excl. breaks)	$	0.55	$

Excl.: excluding, L+C: lapatinib + capecitabine, mBC: metastatic breast cancer, P+T+D: pertuzumab + trastuzumab + docetaxel, T+D: trastuzumab + docetaxel, T-DM1: trastuzumab emtansine
Source: Table 98, pp224-225 of the resubmission, Nerlynx_PBAC_Section3_July2019 workbook

The redacted table shows ICERs in the range of $15,000/QALY – more than $200,000/QALY.

Drug cost/patient/course

6.49 The cost per patient per course would be $ for patients who use a dose of 240 mg daily for the full 12 month course. The cost per patient per course based on trial data, presented in the economic model, and from the financial estimates is shown in Table 16. The model calculated the drug cost by multiplying the monthly cost by the proportion disease free for the duration of 8.1 months, however the mean duration

(of 8.1) already accounts for the discontinuation of patients who have progressed. A corrected model cost is presented below.

Table 16: Drug cost per patient for neratinib

	Trial dose and duration	Model	Financial estimates
Mean dose	210.4 mg/day[a]	210.4 mg/day[a]	240 mg/day
Mean duration	8.23 months	8.10 months[b]	8.58 months[c]
Total mg administered	54,194 mg[d]	51,117 mg[e*]	61,776 mg[e*]
Cost/patient/month	$[redacted][f*]	$[redacted][f*]	$[redacted][f*]
Cost/patient/course	$[redacted][g*]	$[redacted] $[redacted][h*]	$[redacted][ij*]

***** calculated during the evaluation.
[a] actual dose intensity in the trial (actual cumulative dose divided by the treatment duration)
[b] mean treatment duration for HR+ patients who have completed trastuzumab within 12 months
[c] assumes 100% of patients receive 2 months treatment. 27% discontinue after 2 months. For patients remaining on therapy, 63.1% remain on 240 mg/day, 18.3% receive 200 mg/day, and 18.5% receive 160 mg/day from month 3 until month 12.
[d] cumulative actual dose in the trial
[e] calculated from mean dose and duration for comparison with trial cumulative actual dose
[f] mean dose x cost per mg x 30 days
[g] cost per mg x total mg administered
[h] correcting the method of drug cost calculations so that the cost per patient per course is the cost per patient per month x mean duration
[i] cost/patient/month x mean duration.
[j] assumes that tablets in the remainder of month are wasted, rather than a cost per tablet

6.50 The proposed DPMQ of neratinib in the resubmission is $[redacted]. The original submission proposed a price of $[redacted].

6.51 The mean dose in the resubmission model is 210.4mg/day, which is consistent with the mean dose observed in the trial. The original submission presented a mean dose of 214.3 mg/day which was the prescribed dose intensity in the trial. This change is appropriate however dose intensity observed in the ExteNET trial may differ from clinical practice.

6.52 The mean duration of treatment in the resubmission financial estimates is 8.58 months, calculated by assuming all patients completed 2 months therapy, then applying discontinuations and dose reductions observed in the ExteNET trial safety population. This was inconsistent with the method used in the economic model.

Estimated PBS usage & financial implications

6.53 The original March 2019 submission was considered by DUSC. A combined epidemiological and market share approach was used. The majority of key sources and assumptions are unchanged from the original submission.

6.54 The number of patients treated and scripts dispensed has changed from the original submission due to differences in parameter values. The resubmission outlined a changed proposed clinical management algorithm reflecting a shift to neoadjuvant treatment, which was not reflected in the estimated use and financial impacts. This made the estimated use and financial impacts uninformative. The PBAC considered

that the changing clinical management algorithm means that the remaining relevant patient populations are diminishing and the estimates are therefore overestimated.

6.55 The total net financial cost for the Australian Government was estimated to be more than $100 million over 6 years. Table 17 presents the estimated use and financial implications of listing neratinib. The resubmission incorporates aggregate output from the economic model as 'modelled costs' that affect PBS, MBS and hospital budgets.

Table 17: 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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of neratinib						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for loperamide						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Modelled costs	–$[redacted]	–$[redacted]	–$[redacted]	–$[redacted]	–$[redacted]	–$[redacted]
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]*	$[redacted]*	$[redacted]*	$[redacted]*	$[redacted]*	$[redacted]*
Net cost to health budget	$[redacted]*	$[redacted]*	$[redacted]*	$[redacted]*	$[redacted]*	$[redacted]*

[a] Assuming 8.58 scripts per patient per year as estimated by the resubmission.
[b] Output from the cost utility analysis is included as an aggregated cost offset in the budget impact model. These costs include endocrine treatment, adverse event management, subsequent therapies and disease monitoring and combine PBS, MBS and hospital costs
*The reported cost of outpatient MBS services was calculated using the May 2019 MBS 85% benefit. This was updated during evaluation to reflect the July 2019 85% benefit
Source: Tables 103 & 112, pp 234 & 241 of the resubmission.

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

6.56 The following key assumptions were not changed from the initial submission:

- The number of patients eligible for treatment is likely overestimated. The resubmission includes the number of patients who initiated trastuzumab in 2018 and data from published literature to estimate the number of eligible incident and prevalent patients. The DUSC previously considered this method was likely to overestimate the number of patients electing treatment with neratinib (paragraph 6.65, neratinib PSD, March 2019). This issue was not addressed in the resubmission.
- The number of patients electing treatment is likely to be overestimated. The resubmission assumed an uptake rate of 60% in Year 1 (2020) increasing to 80% in Year 3 and beyond. DUSC previously considered the uptake rate would be 60% across

all estimate years (paragraph 6.66, neratinib PSD, March 2019). This issue was not addressed in the resubmission.

6.57 The resubmission estimated the number of neratinib prescriptions using a weighted average treatment course per patient of 8.58 prescriptions This is not consistent with the economic model, which applies a mean treatment duration of 8.1 months and relative dose intensity of 88%, equivalent to 7.10 prescriptions.

6.58 The resubmission did not consider an alternative scenario in which the near market comparators pertuzumab and T-DM1 were listed prior to or in parallel with neratinib. DUSC previously considered that there is evidence that the near market competitor T-DM1 in the post-neoadjuvant setting is more effective than neratinib and that if T-DM1 is listed on the PBS for this indication the uptake of neratinib would be greatly reduced (paragraph 6.68 neratinib PSD, March 2019). The uptake of neratinib in this scenario is uncertain. The PSCR provided an updated financial model to account for the possible listing of T-DM1 on the PBS, however the ESC noted that the updated financial model contained errors that overestimated the number of patients receiving trastuzumab for eBC and overestimated the cost offsets associated with modelled costs.

6.59 The total cost offset due to 'modelled costs' derived from the economic evaluation over six years is $60 - $100 million. The ESC noted the offsets used in the model were uncertain given the model issues discussed above and therefore introduced additional uncertainties to the financial estimates. Additionally, changes in use and financial impact of individual treatments for adverse events (other than loperamide), endocrine treatments and subsequent treatments for local and distant/metastatic recurrence were not presented and could not be verified. Changes in units and costs of affected MBS items are not presented and could not be verified.

6.60 The ESC considered the resubmission did not adequately address the PBAC's concerns raised in the original submission regarding market size, uptake rate and the change in approach to treating high risk HER2+ patients.

Quality Use of Medicines

6.61 The resubmission provided details from the European Union Risk Management Plan (EU RMP) and the Australian Specific Annex (ASA). The EU RMP and ASA have been updated since the original submission. Neratinib was registered by the TGA on 15 March 2019, subject to conditions described in the EU RMP and ASA. The updated documents were not provided in the resubmission.

6.62 The resubmission describes additional risk-minimisation activities to be undertaken in Australia, including the development and distribution of physician education material and patient information booklets. The materials will be distributed in-person to oncologists, provided as electronic or hard copy upon request by patients and HCPs,

and available to HCPs on the sponsor's website. The pre-PBAC response noted that the sponsor is committed to maintaining the existing patient support program, which involves intensive weekly calls for the first 5 weeks to mitigate any potential adverse events, followed by monthly calls for the remainder of treatment.

6.63 No post-marketing surveillance studies were proposed by the resubmission. This is unchanged from the original submission. Considering neratinib use is associated with high rates of diarrhoea, a surveillance program monitoring the regimens and management of diarrhoea should have been included.

Financial Management – Risk Sharing Arrangements

6.64 The resubmission proposed an in-principle risk-sharing arrangement (RSA) whereby a rebate of [redacted]% of the cost of neratinib would be paid for any usage beyond the eligible patient population (100% uptake). This is unchanged from the original submission. The DUSC and ESC previously noted that the RSA proposed in the submission was for [redacted]% rebate above the eligible population rather than the estimated population. The ESC maintained that this would not provide certainty in terms of the financial impact of listing neratinib given the estimated patient numbers in the resubmission were uncertain (paragraph 6.71, neratinib PSD, March 2019). The resubmission did not address this issue. The ESC considered an RSA with a 100% rebate above agreed caps may mitigate uncertainties around patient numbers and uptake, however this would still require that the clinical place and cost-effectiveness of neratinib be established.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of neratinib for extended adjuvant treatment of adult patients with HER2+, HR+ eBC who have completed prior adjuvant trastuzumab-based therapy within the past 12 months. The PBAC considered that the clinical place of neratinib was reduced to a limited and diminishing population, given the changing landscape for the treatment of HER2+ eBC. The PBAC noted that the resubmission had provided limited or no evidence for some patient groups. For the remaining relevant patient groups where evidence was presented, the PBAC considered that the benefit of neratinib was likely to be small, and the economic model had not provided a reliable basis for estimating the cost-effectiveness of neratinib in these patients.

7.2 The PBAC noted that input from 37 individuals and two organisations (BCNA and MOGA) was received in support of a PBS listing for neratinib. The BCNA noted that there was increasing use of neoadjuvant treatment in eBC however believed that there would be a patient population, albeit a small population, who would benefit from treatment with neratinib in the adjuvant setting following trastuzumab

treatment. The comments also noted that despite the side effects, being able to prevent the return of cancer was a significant priority for patients and that many patients would be prepared to tolerate the side effects in order to gain greater benefit in the long term. The sponsor hearing stated that dose escalation together with the patient support program has helped patients and oncologists manage the adverse events associated with neratinib. The PBAC considered that the comments indicated that consumers were well-informed about the adverse effects associated with treatment with neratinib.

7.3 The PBAC considered the fundamental issue was that the resubmission had not outlined a clear clinical place for neratinib in eBC therapy. The PBAC noted that the resubmission included a revised clinical management algorithm incorporating the likely clinical place of emerging therapies pertuzumab and T-DM1, but considered that the clinical place for neratinib was inconsistently applied across the resubmission.

7.4 As outlined in Table 3 ('Population and disease' section) and the paragraphs below, the PBAC considered that the clinical place for neratinib was highly limited and likely to be diminishing due to the changing landscape of HER2+ breast cancer treatment and the paucity of data in many of the remaining patient populations. The PBAC considered that the treatment algorithm for early breast cancer treatment was changing because patients with a high risk of disease recurrence, such as those with ≥T1c/N+ tumours would most likely be treated with neoadjuvant therapy. Patients with residual disease following neoadjuvant therapy would most likely be treated with adjuvant T-DM1 given the higher iDFS benefit across the ITT and all subgroups as demonstrated in the KATHERINE trial.

7.5 The PBAC considered that limited or no data was presented to support use of neratinib in the following patient groups/places in therapy:

- following T-DM1 or in patients who discontinue T-DM1 (no data was presented for these patients as the ExteNET trial only included patients who received prior trastuzumab). As noted in the paragraph above, the PBAC considered that, if T-DM1 were to become available, a large proportion of high risk patients would receive T-DM1.
- patients with pCR following neoadjuvant treatment (limited data presented as these patients were excluded in Amendment 3 of the trial; only 4.4% of patients in the ITT population of the ExteNET trial had pCR following prior neoadjuvant therapy); and
- patients with T1a/bN0 tumours following adjuvant treatment (no data presented as these patients were excluded from the ExteNET trial).

Thus, the PBAC considered that the clinical benefit of neratinib was unknown in these patient groups and considered that, based on the evidence presented in the resubmission, neratinib would not be suitable for listing in these patient groups.

7.6 The PBAC considered that the remaining potentially relevant population, in whom neratinib may have a clinical place, was limited to two groups:

- patients with residual disease following neoadjuvant treatment who have already begun adjuvant treatment with trastuzumab. The PBAC considered this patient group is likely to quickly diminish, and will be limited to prevalent patients, if T-DM1 is listed on the PBS for this indication.
- patients with ≥T1cN0-3 tumours who do not undergo neoadjuvant treatment. The PBAC considered that this patient group is also likely to diminish given the shift to neoadjuvant treatment, as also noted by the BCNA.

7.7 Overall, the PBAC considered that the appropriate clinical place for neratinib was limited to a small and diminishing group of patients (prevalent patients with residual disease following neoadjuvant treatment who have already begun adjuvant trastuzumab, and patients with ≥T1cN0-3 tumours who do not undergo neoadjuvant treatment). The PBAC expressed concern that, for some patients, availability of neratinib following adjuvant trastuzumab could encourage a treatment pathway associated with minimal or no incremental benefit and worse adverse events compared to alternate treatment pathways.

7.8 The PBAC maintained its views from its previous consideration that the nominated comparator of usual care/placebo was reasonable. The PBAC noted that pertuzumab was presented as a near market comparator. While the PBAC considered that a comparison against T-DM1 was unnecessary, given the different clinical places of the two therapies, the PBAC considered that the submission should have better accounted for the clinical place of neratinib if T-DM1 becomes available (as discussed above).

7.9 The resubmission was based on the same clinical evidence presented in the original submission: one head-to-head randomised trial comparing neratinib to placebo (N=2,840): ExteNET trial. The resubmission also conducted an indirect comparison of neratinib (ExteNET trial) and pertuzumab (APHINITY trial), using trastuzumab plus chemotherapy (T+Chemo) as the common comparator. The PBAC considered that the indirect comparison was unreliable because of the applicability and exchangeability issues across the two trials and noted that the indirect comparison was likely to favour neratinib.

7.10 The resubmission did not present OS data, as previously requested by the PBAC (paragraph 7.17, neratinib PSD, March 2019). The PBAC considered that without OS data the long term benefits of neratinib therapy are unknown. The PBAC noted that the resubmission stated that OS data for the ITT population of the ExteNET trial will be available in the first half of 2020, though OS data for the HR+ subset will not be available until 2024-2027.

7.11 Overall, the PBAC maintained its views from its previous consideration that the difference in iDFS was small (2.5% risk difference for iDFS at 5 years in the ITT

population, with 90.2% and 87.7% of patients being invasive disease-free in the neratinib and placebo arms, respectively) and uncertain given the potential for a high risk of bias due to protocol amendments, the reliance on a subgroup of the ExteNET trial, and potential applicability issues with the trial relating to underrepresentation of node negative patients and the prior neoadjuvant and adjuvant treatments used.

7.12 The PBAC considered that in the remaining relevant population (as identified in Paragraph 7.6), the treatment effect was likely to be lower than observed in a broader trial population, as patients treated with neratinib will likely be at lower risk if T-DM1 is preferentially used to treat higher risk patients.

7.13 As noted in the original submission, the PBAC considered that the AE data for neratinib compared to placebo showed a clear pattern of increased risk of serious treatment related TEAE, including those leading to withdrawal of treatment or dose reductions. The PBAC further considered that the diarrhoea will impact on the attrition levels in clinical practice and therefore on treatment effectiveness. As noted above, the PBAC considered that the patient support program appears to have helped patients and oncologists manage the adverse events associated with neratinib. However, the PBAC maintained its view that the adverse events experienced with neratinib therapy compared to placebo were significant and may outweigh the small benefit for some patients.

7.14 The resubmission presented a cost-utility analysis comparing neratinib to usual care based on the ExteNET trial, Australian mortality data and data from published literature. Although some of the PBAC's previous concerns were addressed, not all issues were addressed by the resubmission. Overall, the PBAC considered the base case presented in the resubmission was highly optimistic due to assumptions and inputs that favoured neratinib. Further, the PBAC considered that a key issue was that the economic evaluation did not reflect use in the small remaining relevant population likely to use neratinib in clinical practice. In particular, the efficacy of neratinib in the remaining relevant population may be lower than assumed in the model. The iDFS benefit in the model was based on the subgroup of patients in the ExteNET trial with HER2+, HR+ disease who completed trastuzumab within 12 months; however, the treatment effect in practice will likely be lower (i.e. as use over time will be limited to a lower risk population if T-DM1 is preferentially used to treat higher risk patients).

7.15 The PBAC noted and agreed with the other issues regarding the economic model that were identified by the evaluation and the ESC (as outlined in the 'Economic analysis' section), particularly the following issues:

- The model incorporated a substantial gain in OS despite no OS data from the ExteNET trial being presented;
- Transition probabilities were based on extrapolation functions fitted to Kaplan-Meier data for the entirety of the model. The PBAC previously expressed a preference for the use of observed data where available.

- The ICER was highly sensitive to the iDFS extrapolation function and assumed duration of treatment effect. The ICER increased from a base case of $45,000/QALY - $75,000/QALY gained to $75,000/QALY - $105,000/QALY with a generalised gamma function.
- There was substantial missing data for utilities sourced from ExteNET as patients who discontinue treatment are not included. Both trial and literature-based utility sources may have overestimated the utility values, favouring neratinib.
- The cost of neratinib was underestimated.
- The duration of subsequent treatment following recurrence was likely overestimated, favouring neratinib.
- The age of clinical trial patients is consistently below the age observed for women with eBC in Australia and therefore not representative of the specific women to whom the requested listing would apply.

7.16 In light of these uncertainties, along with the small iDFS benefit and unclear OS benefit, the PBAC considered that the ICERs presented were unacceptably high and not consistent with the previously recommended ICERs for other adjuvant breast cancer therapies. The PBAC considered that a clear clinical benefit would need to be demonstrated with neratinib in the relevant populations for it to be evaluated for cost-effectiveness.

7.17 The PBAC considered that the estimated financial impact of neratinib to the Australian Government was likely substantially overestimated in the resubmission given that the population that is likely to benefit from neratinib would be a limited and diminishing population given the changing landscape for the treatment of HER2+ eBC. The PBAC considered the resubmission did not adequately address the PBAC's concerns raised in the original submission regarding market size, uptake rate and the change in approach to treating high risk HER2+ patients.

7.18 The PBAC considered that any potential resubmission would need to be for the patient groups for whom there is both a clinical place and clinical evidence for neratinib. The PBAC considered that this would be a small and diminishing group of patients, who would likely be at lower risk and derive a lower clinical benefit than observed in the broader trial population. The PBAC therefore considered that a resubmission may not be feasible, as it would need to include clear clinical data for the population defined in Paragraph 7.6, with associated changes to the model and financial estimates.

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.