5.05 NERATINIB, Tablet 40 mg, Nerlynx®, Specialised Therapeutics PM Pty Ltd.

1 Purpose of Application

1.1 Authority Required listing for neratinib for treatment of adult patients with human epidermal growth factor receptor 2 (HER2) positive, hormone receptor positive (HR+), early breast cancer (eBC) who have completed prior adjuvant trastuzumab based therapy within the past 12 months.

1.2 The basis of listing was cost-effectiveness of neratinib compared to placebo.

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

Component	Description
Population	Adult patients with HER2+, HR+, eBC who have completed prior adjuvant trastuzumab based therapy within the past 12 months
Intervention	Neratinib 240mg (6 x 40mg tablets) taken orally once daily, continuously for one year
Comparator	Usual care/placebo
Outcomes	Invasive disease-free survival (primary outcome), distant disease-free survival, time to distant recurrence, incidence of CNS recurrence, adverse events
Clinical claim	Neratinib is more effective than placebo at improving invasive disease-free survival. Neratinib is inferior in terms of safety compared with placebo.

CNS: central nervous system, HER2+: human epidermal growth factor receptor 2 positive; HR+: hormone receptor positive; eBC: early breast cancer
Source: Table 2, p2 of the submission.

2 Requested listing

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

Initial treatment

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
NERATINIB 40 mg tablet Initial therapy	1	180	1	$[redacted]	Nerlynx, Specialised 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
PBS Indication:	Early HER2~~+~~ *positive* breast cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	☒~~Authority Required - In Writing~~ ☒*Authority Required - Telephone*
Clinical criteria:	~~Patients must have completed a course of prior adjuvant trastuzumab-based therapy AND~~ ~~Patients must have received last dose of trastuzumab >2 weeks and <52 weeks before initiation of neratinib~~. *Patient must have 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 AND ~~Patient must have evidence of hormone receptor (HR) positive status~~ *The condition must be hormone receptor positive* AND The treatment must be the sole PBS-subsidised anti-HER2 therapy *for this condition* *AND* *Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy for this drug for this condition*
~~Prescriber Instructions~~	~~Authority applications for initial treatment must be made in writing and must include:~~ ~~(a) a completed authority prescription form; and~~ ~~(b) a completed Early Breast Cancer - PBS Supporting Information Form which includes:~~ ~~(i) a copy of the pathology report from an Approved Pathology Authority confirming of hormone receptor (HR) positive status; and~~ ~~(ii) a copy of the signed patient acknowledgement form.~~
Administrative Advice	~~Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).~~ ~~Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au~~ ~~Applications for authority to prescribe should be forwarded to:~~ ~~Department of Human Services~~ ~~Prior Written Approval of Complex Drugs~~ ~~Reply Paid 9826~~ ~~GPO Box 9826~~ ~~HOBART TAS 7001~~ *No applications for increased maximum quantities will be authorised.* *No applications for increased repeats will be authorised.*

Source: Table 8, p15 of the submission.

Continuing treatment

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
NERATINIB 40 mg tablet Continuing treatment	1	180	~~24~~	$[redacted]	Nerlynx, Specialised 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
PBS Indication:	Early HER2~~-~~ *positive* breast cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	☒Streamlined
Clinical criteria:	Patient must have previously ~~been issued with an authority prescription for~~ *received PBS-subsidised treatment with* this drug for this condition, AND Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy *for this drug for this condition*. AND The treatment must be the sole PBS-subsidised anti-HER2 therapy *for this condition.*
Prescriber Instructions	*A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.*
Administrative Advice	~~Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).~~ *No applications for increased maximum quantities will be authorised.* *No applications for increased repeats will be authorised.*

Source: Table 9, p16 of the submission.

Grandfathering treatment

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
NERATINIB 40 mg tablet Initial therapy	1	180	1	$[redacted]	Nerlynx, Specialised 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
PBS Indication:	Early HER2 positive breast cancer
Treatment phase:	Grandfathering treatment
Restriction Level / Method:	☒Authority Required - Telephone
Clinical criteria:	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition before <Date of Listing> AND The treatment must be the sole PBS-subsidised anti-HER2 therapy *for this condition*. *AND* *Patient must have been treated with a course of adjuvant trastuzumab within 12 months of initiating non-PBS subsidised treatment with this drug for this condition* AND *Patient must not have local or regional recurrence of disease or metastatic disease* AND *The condition must be hormone receptor positive* *AND* *Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy for this drug for this condition*
Prescriber Instructions	*A patient may qualify for PBS-subsidised treatment under this restriction once only.* *For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.*
Administrative Advice	~~Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).~~ *No applications for increased maximum quantities will be authorised.* *No applications for increased repeats will be authorised.*

Source: Table 10, p17 of the submission

2.1 The ESC noted the requested restriction is narrower than the proposed TGA indication. The TGA indication is for patients with HER2+ eBC, without reference to HR status. The proposed PBS restriction included a more restricted patient population: HER2+, HR+, eBC.

2.2 The pre-PBAC response agreed with the following changes to the proposed restrictions:

- a streamlined restriction level for continuing treatment, especially as trastuzumab for eBC is Authority Required (Telephone). This aligned with DUSC advice.

- simplifying the clinical criterion in the initial restriction to "Patient must have been treated with a course of adjuvant trastuzumab-based therapy within the last 12 months prior to initiating treatment with this drug for this condition."
- including administrative advice regarding the requirement for concurrent administration of anti-diarrhoeal prophylaxis as advised by the ESC. The Pre-Sub-Committee Response (PSCR) noted that anti-diarrhoeal medication (loperamide) will be mandated in the Australian Product Information for the first two cycles.

2.3 The pre-PBAC response disagreed with the DUSC advice that the PBS criteria should specify that the only prior PBS funded HER2 therapy should be trastuzumab. The pre-PBAC response argued that patients who have been treated with other HER2+ agents such as pertuzumab or trastuzumab emtansine (T-DM1) should not be excluded from accessing neratinib as this would not allow clinicians the freedom to select the best course of therapy for their patients. The PBAC considered that it was not appropriate to allow neratinib treatment following pertuzumab or T-DM1 as the clinical benefit in this population is unknown. See also paragraph 4.4 and 4.5 below.

2.4 Table 2 compares the proposed PBS listing and the populations in the ExteNET trial. The ExteNET trial reported data for 2 populations:

- The intent to treat (ITT) population which included all randomised patients; and
- The amended ITT population (aITT) which included all patients randomised after global amendment 3, which revised the eligibility criteria to include patients with Stage 2 to 3c, node-positive breast cancer, who had completed prior trastuzumab therapy within 1 year. The aITT population also included all patients randomised prior to implementation of amendment 3 if they met the following key criteria: 1. node-positive disease and 2. randomised within 1 year from completion of prior trastuzumab therapy.

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

Factor	Proposed PBS listing	ITT trial population	aITT trial population
Stage 1 included	Yes	Yes	Unclear: stage 1 excluded if enrolled after amendment 3
Last trastuzumab dose	≤1 year	≤2 years	≤1 year
Neoadjuvant trastuzumab therapy	Not PBS listed in eBC	Allowed	Allowed
Nodal status	+/-	+/-	+
HR status	+	+/-	+/-

Compiled during the ESC evaluation
eBC: early breast cancer; PBS: Pharmaceutical Benefits Scheme

2.5 The ESC considered that the requested restriction is not consistent with the ExteNET trial presented in Section 2:

- The ExteNET trial (ITT and aITT population) included patients with either HR+ or HR- disease. However, the proposed PBS indication only includes patients with HR+ disease. The PSCR argued the pre-specified subgroup analysis of HR+ patients in the ITT population most closely matched the proposed PBS population.
- The ExteNET trial (ITT population) included patients who completed neoadjuvant or adjuvant trastuzumab therapy up to two years prior to randomisation. However, the proposed PBS indication and aITT population only include patients who completed adjuvant trastuzumab therapy up to one year prior to initiation of neratinib. The ESC noted that 80.9% of patients in the ITT group had completed trastuzumab ≤1 year from randomisation, therefore, the majority of patients were aligned with the proposed PBS population in terms of the time since trastuzumab therapy.
- Part of the ITT population of the ExteNET trial (after protocol amendment 3) excluded subjects with Stage 1 disease. However, the proposed PBS indication includes patients with Stage 1 disease.
- Part of the ITT population of the ExteNET trial (after protocol amendment 3) and the aITT population only included patients with node-positive disease. Consequently, 77% of patients were node-positive in the ITT population of the ExteNET trial. The ESC considered that there was no clinical rationale for excluding node negative patients and that it was not reasonable to do so as there may be some high risk node negative patients who may benefit from treatment with neratinib. The ESC noted that the minutes from the Advisory Board meeting identified patients with a tumour size greater than 2.1 cm and/or patients who failed to respond to neoadjuvant therapy as possible high risk node negative patients. The ESC noted that it was unknown what proportion of patients included in the ExteNET trial or in the proposed PBS population would fall into this category.
- The ExteNET trial included patients who were immunohistochemistry (IHC3+) or in situ hybridization (ISH+) for HER2. However, trastuzumab (for eBC) is PBS listed for patients who are HER2+ on the basis of the ISH test only. The PSCR argued that an Australian study reported there is a low rate of discordance (1.2%) between IHC and ISH assays (Balasubramanian, 2018). The ESC noted the reference provided was a conference abstract based on a retrospective analysis and the risk of bias could not be determined.

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

3 Background

Registration status

3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, neratinib was TGA approved for "the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab based therapy".

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

4 Population and disease

4.1 Breast cancer is the most frequently diagnosed malignancy in women and the leading cause of cancer mortality in women worldwide. In Australia, 16,753 people were diagnosed with breast cancer, and 2,868 died as a result of breast cancer, in 2014 (AIHW 2017).

4.2 HER2 is a transmembrane receptor tyrosine kinase, involved in mediating growth, differentiation and survival of cells. HER2+ breast cancer has an increased tendency to metastasis and a poorer prognosis (Slamon et al, 2011). In Australia approximately 15% of breast cancer patients are HER2+ (Bilous 2012a) (based on ISH testing).

4.3 75% percent of all breast cancers are HR+ with overexpression of oestrogen receptors (ER) and/or progesterone (PgR) receptors. Around 50% of all HER2+ breast cancer is HR+. A prospective cohort study showed that HER2+, HR+ breast cancer is associated with a constant risk of relapse overtime, whereas HER2+, HR- breast cancer is associated with a higher risk of early recurrence (Schettini et al., 2016).

4.4 The 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 considered this treatment algorithm to be appropriate in the absence of pertuzumab for eBC on the PBS. However, the ESC noted it was uncertain whether (if PBS listed) use of pertuzumab would negate the clinical benefit of neratinib in this population. The PBAC noted there is limited data regarding the benefits of neratinib after treatment with pertuzumab.

4.5 The PBAC noted that there is a move towards neoadjuvant therapy in patients with high risk eBC. This approach allows assessment of response to therapy at the time of surgery. A recent large meta-analysis of eBC trials with neoadjuvant chemotherapy[1] reported the prognostic importance of pathological complete response (pCR), which correlates with event free and overall survival. The PBAC noted data from the KATHERINE trial[2] demonstrated that patients with residual invasive disease after completing neoadjuvant chemotherapy + trastuzumab, who were then treated with T-DM1, had a 50% lower risk of recurrence of invasive breast cancer or death than patients treated with trastuzumab alone. The KATHERINE study supports a change in the treatment pathway in the adjuvant setting, particularly for high risk patients. The

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

[2] von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019 Feb 14;380(7):617-628. doi: 10.1056/NEJMoa1814017.

PBAC noted no data was presented of the effectiveness of neratinib after treatment with T-DM1.

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

5 Comparator

5.1 The submission nominated usual care/placebo as the main comparator (p7 of the submission). The PBAC considered this was reasonable.

5.2 Pertuzumab in combination with trastuzumab and chemotherapy (Ptz+T+Chemo), also considered by the PBAC at the March 2019 meeting, is a potential near market comparator as there are no data to support Ptz+T+Chemo in Year 1 followed by neratinib in Year 2, and hence the addition of pertuzumab in year 1 and the use of neratinib in year 2 are alternative treatment options. The PSCR argued that pertuzumab is not a near market comparator for neratinib on the basis that it is used in an earlier line of therapy and would most likely be used in a HR- population. The PBAC considered that Ptz+T+Chemo is a relevant near market comparator because, without evidence of the clinical benefit for sequential treatment with neratinib after pertuzumab, sequential use is not considered to be appropriate.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician reiterated facts from the submission regarding the study design and outcomes of the primary clinical trial ExteNET. The PBAC did not consider this information to be new or helpful to its deliberations.

6.2 The clinician noted that diarrhoea is the main adverse event experienced, which occurred in the first 2 months of starting neratinib treatment and reduced during treatment. The CONTROL trial data presented in the submission showed that administration of colestipol, a bile acid sequestrant, as an add-on to loperamide prophylaxis treatment was effective at reducing diarrhoea events in patients treated with neratinib compared to treatment with loperamine alone. The PBAC considered that colestipol may not be an appropriate anti-diarrhoeal treatment because of its adverse event profile and the potential to affect absorption of neratinib. The PBAC also noted that the proposed prophylaxis is in addition to an already considerable pill burden associated with neratinib.

6.3 The clinician addressed other matters in response to the Committee's questions such as confirming that there is a shift in treatment management of HER2+ patients towards a neoadjuvant approach, based on individual treatment goals. The clinician highlighted that neratinib showed clinical benefit in patients treated with neoadjuvant chemotherapy + trastuzumab, compared to placebo in the ExteNET trial.

6.4 The clinician noted that the treatment effect of neratinib attenuated over time in the ITT population and that this may be due to the inclusion of HR- patients who are at higher risk of early recurrence. However, in HR+ patients, neratinib reduced the risk of recurrence at 3 and 5 years after commencing treatment.

Consumer comments

6.5 The PBAC noted and welcomed the input from individuals (3), health care professional (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with neratinib including that it is an oral treatment which can cross the blood brain barrier. Although there are known side effects, consumers considered these side effects could be managed through prophylactic medication on initiation of neratinib treatment.

6.6 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) highlighting the likely use of neratinib in clinical practice, despite the known side effects. The PBAC noted the advice that neratinib being in oral form made it easier for combination treatment with aromatase inhibitors, the adverse event of diarrhoea was transient and manageable, and that neratinib would prevent early stage disease from progressing to metastatic disease.

6.7 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)[3], based on a comparison with placebo.

Clinical trials

6.8 The submission was based on one head-to-head randomised trial comparing neratinib to placebo (N=2,840): ExteNET.

6.9 Table 3 presents the details of the trial presented in the submission.

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

Table 3: Trials and associated reports presented in the submission

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 early-stage HER2+ breast cancer: Correlative analyses of 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.
	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.

Trial ID	Protocol title/ Publication title	Publication citation
	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. Wang M., Tao Z. Safety and efficacy profile of neratinib in breast cancer: Pooled reanalysis based on randomized controlled trials.	San Antonio Breast Cancer Symposium, SABCS 2017. United States. 78 (4 Supplement 1) (no pagination), February 2018. 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 12, p23 of the submission

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

Table 4: 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 prior to randomisation Amendment 3: HER2+, HR+ & HR-, lymph node positive eBC; completed trastuzumab up to 1 year prior to randomisation	Primary outcome: iDFS of the ITT population[a], aITT population[b], Centrally-confirmed ERBB2-positive[c]. 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; iDFS: invasive disease free survival; 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);

[a] ITT: Intent to treat: The ITT population includes all randomised patients with the exceptions documented in the statistical analysis plan (SAP). Patients were analysed by the randomised treatment arms regardless of the actual treatment received.

[b] aITT: amended Intent to treat: The aITT population includes all patients randomised under global amendment 3 or later amendment, and patients randomised prior to implementation of global amendment 3 if they met the following key criteria: 1. patients with node-positive disease and 2. patients randomised within 1 year from completion of prior trastuzumab therapy.

[c] 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 submission

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

6.12 The ESC considered that the overall risk of bias of the ExteNET trial was high for the following reasons:

- Amendment 3 revised the ExteNET trial eligibility criteria to include patients with Stage 2 to 3c, node-positive breast cancer, who had completed prior trastuzumab therapy within 1 year. These changes restricted eligibility to a higher-risk population as previous studies found that 1) patients with node negative disease who received trastuzumab-based chemotherapy have a lower rate of recurrence

compared with node positive disease and 2) patients are at higher risk of recurrence closer to completion of adjuvant trastuzumab and that the risk of recurrence may decrease over time (Perez et al. 2014; Perez et al. 2011; Slamon et al. 2016). These changes were intended to increase the likelihood of trial success. These protocol amendments may have affected the applicability of the efficacy results, as node-positive patients are likely to be over-represented in the ExteNET trial.

- Two protocol amendments (Amendment 9 & 13) revised key statistical analyses methods and the follow-up period. Protocol amendment 9 (14/10/2011) shortened the follow-up period from 5 years to 2 years. Protocol amendment 13 (16/1/2014) re-extended the follow-up period from 2 years back to 5 years. Patients who had discontinued follow-up at 2 years were asked to re-consent to obtain survival data from their medical records. 74.5% of patients re-consented. A comparison of the baseline characteristics of the patients who re-consented compared to those who did not re-consent was not provided, and it is unknown if the survival differed for consenting versus non-consenting patients. The PSCR claimed that baseline characteristics were comparable between consented and non-consented patients, however no further evidence was provided to support this statement. The PSCR noted that the iDFS HR at 2 years in non-reconsented patients (0.62, 95%CI: 0.41, 0.92) was comparable to iDFS for the ITT group at 2 years (0.68, 95%CI: 0.51, 0.91 from the PSCR or 0.66, 95%CI: 0.49, 0.90 from the submission). The ESC noted that this issue was most likely to have an impact on outcomes between two and five years rather than at two years and the characteristics of the non-censored patients compared with censored patients is still unknown. The 5-year results may have favoured neratinib if patients who did not re-consent had a worse survival outcome compared with those who re-consented. The amendments to the follow-up period are unlikely to affect the adverse events and quality of life measures given that these outcomes were only measured during the one year course of treatment.
- Patients and investigators are likely to have been unblinded to treatment allocation as 95.4% of patients experienced diarrhoea with neratinib versus 35% with placebo. This is less likely to affect the objective health outcomes such as iDFS, but may bias subjective outcomes, including adverse events and quality of life measures.

6.13 The PSCR stated that changes in the eligibility criteria were carried out to enrich the study population with a higher risk of recurrence to better represent the potential patient population. The ESC considered that although the magnitude and direction of change due to these protocol amendments were not able to be determined, overall they appeared to bias the comparison in favour of neratinib because changes impacted on the proportion of patients with stage 1 and node negative disease and therefore the treatment effect for neratinib was likely to be overestimated.

6.14 The ESC noted the PSCR did not address differences between the populations of the ExteNET trial and the Australian setting such as the proportion of patients with positive lymph node status, the proportion of patients with stage 1 disease, duration of trastuzumab treatment prior to neratinib, or the proportion of patients who received neoadjuvant trastuzumab.

Comparative effectiveness

6.15 Table 5 presents the results of the iDFS for the ITT population, aITT population, and centrally-confirmed receptor tyrosine-protein kinase erbB-2 (ERBB2) positive populations (i.e. HER+ population), and the sensitivity analyses of the iDFS for the ITT population.

Table 5: Results of iDFS of the ExteNET trial across the trials

Population	Neratinib Events: n/N (%) % iDFS (95% CI)	Placebo n/N (%) % iDFS (95% CI)	RD*	P value (log rank test)	Hazard ratio (95% CI)
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) (at 2 years)	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 statistical analysis plan (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.

* Compiled during the evaluation

Source: compiled during the evaluation based on information provided in Table22, p52 of the submission; 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[4]. However, this may fall to Grade C with the availability of OS data if the absolute difference in OS is similar to iDFS[5].

6.17 Figure 1 shows the Kaplan-Meier plot of the iDFS analyses for the ITT population (7 July 2014 analysis) and Figure 2 shows the corresponding data for the 1 March 2017 analysis, following re-consenting of patients (and thus high levels of censoring). The difference in iDFS at 2 years was similar for both analyses.

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%). The ESC considered that the absolute benefit of neratinib in terms of iDFS was small.

6.19 The iDFS results based on 1 March 2017 analysis should be interpreted with caution as the baseline characteristics and survival outcome of the patients who re-consented compared with those who did not re-consent were not provided. The results may have favoured neratinib if patients who did not re-consent had worse survival outcomes than those who did re-consent.

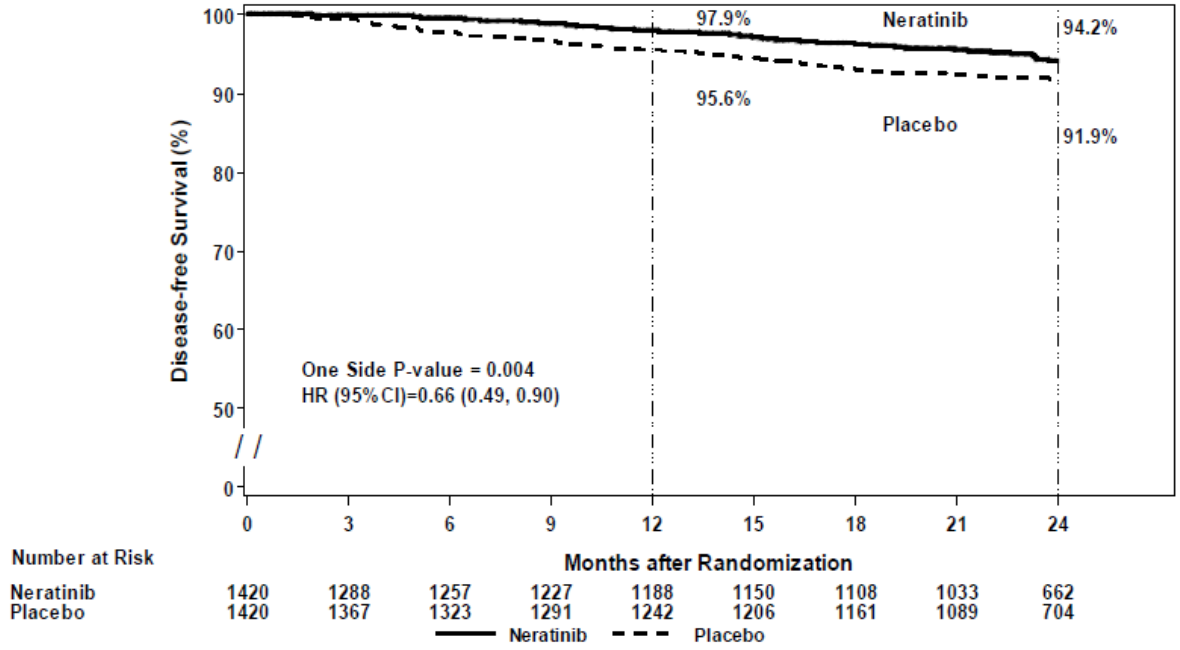
[4] The ESMO MCBS for adjuvant therapy or new potentially curative therapies without mature survival data is defined as follows:

- Grade A: Improvements in DFS alone (primary endpoint) (lower 95% CI of HR <0.65) in studies without mature survival data.
- Grade B: Improvement in DFS alone (primary endpoint) (lower 95% CI of HR 0.65–0.8) without mature survival data.
- Grade C: Improvement in DFS alone (primary endpoint) (lower 95% CI of HR >0.8) in studies without mature survival data.

[5] The ESMO MCBS for adjuvant therapy or new potentially curative therapies with mature survival data is defined as follows:

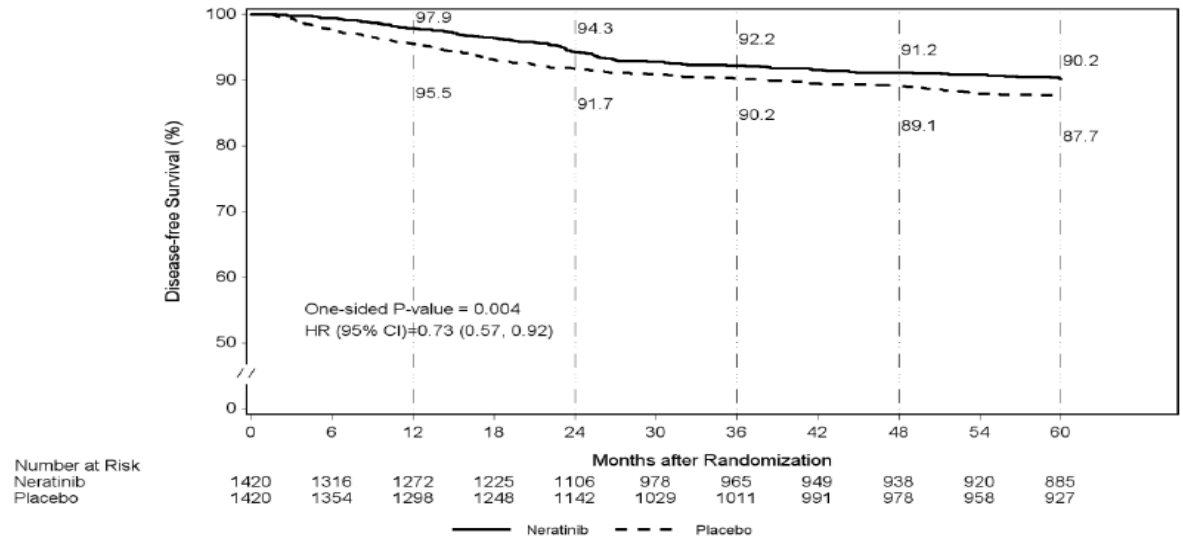
- Grade A: >5% improvement of survival at ≥3 years follow-up.
- Grade B: ≥ 3% but ≤ 5% improvement at ≥3 years follow-up.
- Grade C: <3% improvement of survival at ≥3 years follow-up.

Figure 1: Kaplan-Meier Plot of Disease free survival-ITT population (July 2014 analysis)



Source: Figure 4, p52 of the submission

Figure 2: Kaplan-Meier Plot of 5-year Disease-free Survival (All Data for Censoring), ITT Population (March 2017 analysis)



Source: Figure 5, p53 of the submission

6.20 The difference in iDFS at 2 years (7 July 2014 analysis) in the aITT population (3.0%) was larger compared with the ITT population (2.3%). This is expected, as the aITT population is a higher risk population and hence patients were more likely to experience an event. The HR (0.65, 95% CI: 0.46, 0.92, p=0.007) for the aITT population was similar to that for the ITT population (HR= 0.66, 95% CI: 0.49, 0.90, p=0.004). The

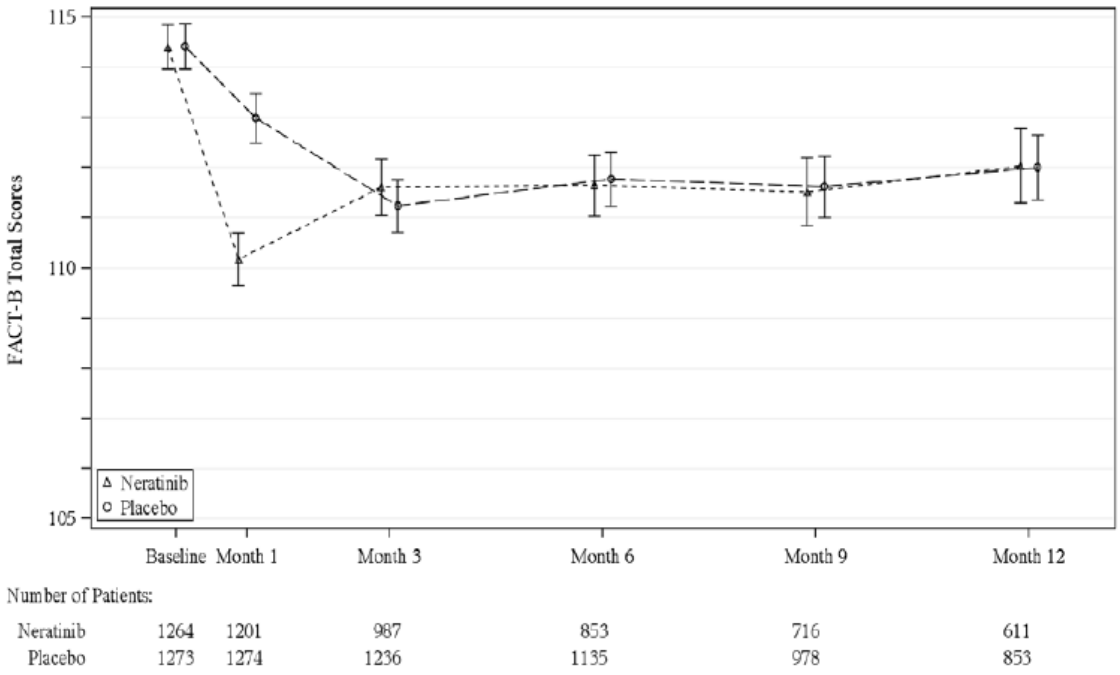
HR (0.51, 95% CI: 0.33, 0.78, p<0.001) was lower for centrally confirmed ERBB2-positive (i.e. HER2+) patients than for the full ITT population.

6.21 There were 130 (10%) patients in the neratinib arm who dropped out of the trial within three months of commencing treatment for reasons other than recurrent disease compared to 44 (3%) patients in the placebo arm.

6.22 The submission stated that OS data are to remain blinded until the requisite 248 deaths are reported and are not expected until late 2019. However, it appeared that OS data for the ITT population were included in the economic model.

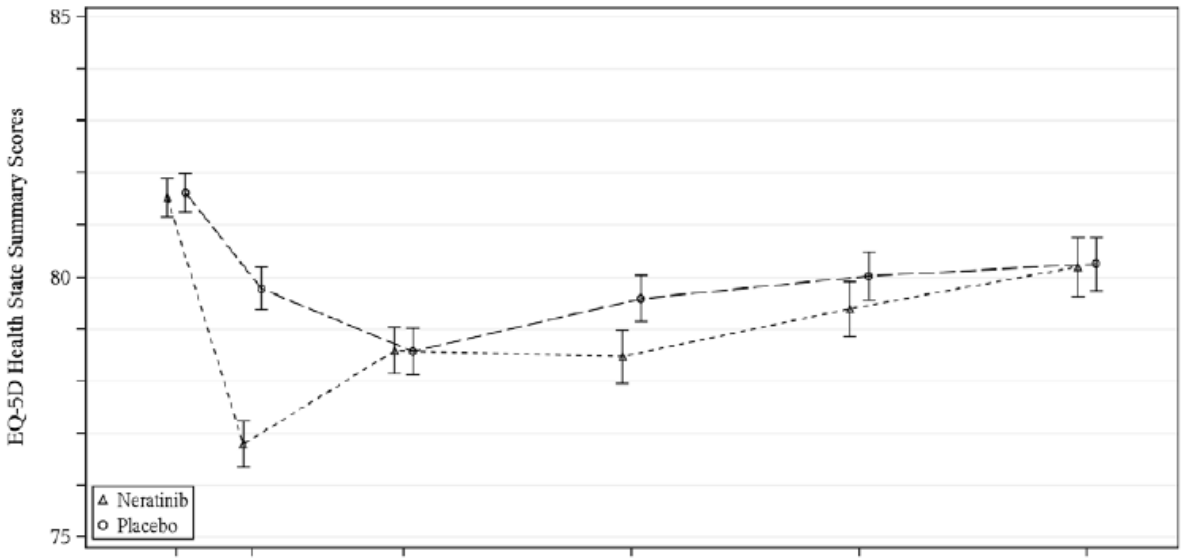
6.23 The average FACT-B total score over time is shown in Figure 3 and the average EQ-5D Health State over time is shown in Figure 4.

Figure 3: Average FACT-B Total Scores Over Time, ITT Population



Source: Figure 8, p61 of the submission

Figure 4: Average EQ-5D Health State Summary Scores Over Time, ITT Population



Number of Patients:

Neratinib	1275	1212	994	856	724	614
Placebo	1277	1285	1243	1140	987	856

Source: Figure 8, p61 of the submission

6.24 The health-related quality of life results over time derived from the EQ-5D instrument were similar to those using the FACT-B instrument. The quality of life results suggested that 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.

6.25 The submission stated that the decreases in FACT-B mean total score (Brady et al, 1997) and in the EQ-5D Health State or Index scores in the first month were not clinically significant.

6.26 The submission proposed PBS listing for HR+ patients. A pre-specified analysis of the HR+ sub-group of the ITT population of the ExteNET trial was presented to support this. The submission argued that several factors may contribute to the superior outcome for HR+ patients:

- The enhanced treatment effect with tyrosine kinase receptors in HR+ can be explained by dual-blockade of bi-directional signalling (cross-talk) between oestrogen receptors (ER) and the HER receptor;

- Clinical data from HR+ subset the "GeparQuinto"[6] and ALTERNATIVE[7] studies externally validates the outcomes observed in Study 3004; and
- Differential efficacy seen in the HR- subgroup may be due to the natural history of disease.

6.27 Table 6 presents the results for the HR+ subgroup analysis.

Table 6: 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

6.28 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 for HR- disease were not statistically significant. The ESC noted that there were nine pre-specified sub-group analyses and questioned whether the significance level for the HR status sub-group analysis should have been adjusted to account for the multiple analyses. The ESC noted the submission did not test whether the treatment effect variation was statistically significant and that the trial was not powered to demonstrate a difference between these subgroups. The PSCR provided results of tests of treatment effect variation which suggested that there was a statistically significant variation by HR status. The ESC also noted that measurement of HR status was not protocol-driven but locally determined. The ESC noted the results indicated that the clinical outcomes were significantly improved for HR+ patients compared to HR- patients.

6.29 The PBAC noted with a median follow-up of 5.3 years the benefit in the HR+ subgroup was greater than that in the HR- subgroup (difference in iDFS at 4 years of 4.1%, HR=0.60 (95% CI: 0.43, 0.83) versus 0.6%, HR=0.95 (95% CI: 0.66, 1.35)), although the test for interaction across the subgroups was not statistically significant (p=0.063).

6.30 The pre-PBAC response noted that the absolute benefit in the patient population who were HR+ and randomised within 1 year from the end of their adjuvant trastuzumab

[6] https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(11)70397-7/fulltext
[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4734643/

therapy had an absolute benefit of 4.5% at 2 years and HR of 0.49 (95% CI: 0.31, 0.75) after 2 years of follow-up.

Comparative harms

6.31 Table 7 presents a summary of patient-relevant harms, based on the ExteNET trial.

6.32 The incidence of diarrhoea (any grade) was higher with neratinib versus placebo (95.4% vs. 35.4%). The incidence of grade 3 or 4 diarrhoea was also higher with neratinib versus placebo (39.9% vs. 1.6%). Diarrhoea was the most common adverse event leading to study discontinuation, observed in 16.8% of patients in the neratinib arm. The ESC 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 ESC noted that the toxicity level of neratinib was high, especially in terms of diarrhoea. The PSCR stated that diarrhoeal prophylaxis was not included in the ExteNET trial, however the CONTROL trial showed that loperamide prophylaxis resulted in a significant reduction in the incidence, severity and cumulative duration of diarrhoea when compared to that observed in the ExteNET trial. The ESC noted that the CONTROL trial indicated that loperamide as prophylaxis had limited impact on the number of patients with grade 3 or 4 diarrhoea (30.7% compared with 39.3% in the ExteNET trial). The ESC also 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 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. The PBAC noted that for patients treated with neratinib 30% had a dose reduction, 44% had a dose hold and 27% discontinued treatment. The PBAC 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.

Table 7: Summary of key adverse events in ExteNET trial

Trial ID	Neratinib n/N (%)	Placebo n/N (%)	RR (95% CI)*
Any TEAE – n (%)	1,387/1,408 (98.5%)	1,240/1,408 (88.1%)	**1.12 (1.10, 1.14)**
Grade 3 or 4 TEAE	700/1,408 (49.7%)	184/1,408 (13.1%)	**3.80 (3.29, 4.40)**
Fatal TEAE	2/1,408 (0.1%)	1/1,408 (0.1%)	2.00 (0.18, 22.03)
Serious TEAE (SAE)	103/1,408 (7.3%)	85/1,408 (6.0%)	1.21 (0.92, 1.60)
Treatment-related TEAE	1353/1,408 (96.1%)	805/1,408 (57.2%)	**1.68 (1.61, 1.76)**
Serious Treatment-related TEAE	42/1,408 (3.0%)	8/1,408 (0.6%)	**5.25 (2.47, 11.14)**
TEAE Leading to Treatment Discontinuation	388/1,408 (27.6%)	76/1,408 (5.4%)	**5.11 (4.04, 6.45)**
TEAE Leading to Study Withdrawal	32/1,408 (2.3%)	7/1,408 (0.5%)	**4.57 (2.03, 10.32)**
TEAE Leading to Dose Reduction	440/1,408 (31.3%)	35/1,408 (2.5%)	**12.57 (8.98, 17.60)**
TEAE Leading to Hospitalisation	93/1,408 (6.6%)	75/1,408 (5.3%)	1.24 (0.56, 0.80)
TEAE Leading to Dose Hold	629/1,408 (44.7%)	187/1,408 (13.3%)	**3.36 (2.91, 3.89)**

CI: confidence interval; n: number of participants reporting data; N: total participants in group;RR: relative risk; SAE: Serious Treatment-emergent adverse events; TEAE: Treatment-emergent adverse events
Bold indicates statistically significant at the 5% level.
Source: Table 30, p67 of the submission
* Estimated during the evaluation

Benefits/harms

6.33 A summary of the comparative benefits and harms for neratinib versus placebo is presented in Table 8.

Table 8: Summary of comparative benefits and harms for neratinib and placebo

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

Harms						
	Neratinib n/N (%)	**Placebo n/N (%)**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Neratinib	**Placebo**	
Grade ≥ 3 TEAE	700/1,408 (49.7%)	184/1,408 (13.1%)	3.80 (3.29, 4.40)	49.7	13.1	36.6% (33.5%, 39.8%)
SAE	103/1,408 (7.3%)	85/1,408 (6.0%)	1.21 (0.92, 1.60)	7.3	6.0	1.3% (-0.6%, 3.1%)
Any grade diarrhoea	1,343/1,408 (95.4%)	499/1,408 (35.4%)	2.69 (2.51, 2.89)	95.4	35.4	59.9% (57.2%, 62.7%)
Any Grade 3 or 4 diarrhoea	562 /1,408 (39.9%)	23/1,408 (1.6%)	24.44 (16.21, 36.83)	39.9	1.6	38.3% (35.6%, 40.9%)

CI: confidence interval; n: number of participants reporting data; N: total participants in group; iDFS: invasive disease free survival; HR+: hormone receptor positive; HR-: hormone receptor negative; HR: hazard ratio; RD: risk difference; RR: relative risk; SAE: Serious Treatment-emergent adverse events; TEAE: Treatment-emergent adverse events; ITT: intent to treat; iDFS: invasive disease free survival; aITT: amended Intent to treat: The aITT population includes all patients randomised under global amendment 3 or later amendment, and 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. Table 19, p121 of the CSR; Figure 17, p79 of the submission
Table 30, p67 of the submission; Table 31, p68 of the submission; Table 32, p69 of the submission.

6.34 On the basis of direct evidence presented by the submission, for every 100 patients treated with neratinib in comparison to placebo:

- At 2 years:
  - Approximately 2-4 additional patients would not experience recurrence (return of invasive disease).
  - Approximately 4 additional HR+ patients would not experience recurrence (return of invasive disease).
- Over a duration of follow up of 24 months:
  - 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, defined as having ≥ 8 diarrhoea episodes per day, possibly requiring hospitalisation.

6.35 The ESC was concerned that for a significant proportion of patients the risk of the adverse events would outweigh the potential benefits of treatment with neratinib. The ESC advised that hospitalisation for dehydration and fluid replacement may be required for grade 3 or 4 diarrhoea, which could eventuate into renal toxicity because of severe dehydration. Although there were up to 4 fewer patients out of 100 who did not experience recurrence, the ESC considered there was uncertainty around the magnitude of this benefit. The ESC also noted that 28% of patients treated with neratinib did not complete treatment due to AEs. The ESC considered, because patients 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.

Clinical claim

6.36 The submission described neratinib as superior in terms of effectiveness and inferior in terms of safety compared with placebo in patients with HER2+, HR+ eBC.

6.37 The ESC 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.

6.38 In terms of comparative safety, the ESC agreed the claim that neratinib is inferior in terms of safety compared with placebo was supported by the clinical data presented.

6.39 The PBAC 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.

6.40 The PBAC considered that the claim of inferior comparative safety was reasonable and consistent with the data. The PBAC considered the adverse events experienced with neratinib therapy compared to placebo were significant and may outweigh the benefit for some patients.

Economic analysis

6.41 The submission presented an economic evaluation based on the ExteNET trial and implemented a modelled evaluation. The type of economic evaluation presented was a cost-utility analysis.

6.42 The submission did not present a stepped economic evaluation.

6.43 Table 9 summarises the model structure and rationale.

Table 9: Summary of model structure and rationale

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Life years gained, Quality-adjusted life years gained
Time horizon	55 years. This is long relative to the 5 year follow-up period of the ExteNET trial. The PBAC previously considered a time horizon of 40 years for trastuzumab for eBC. [8]
Methods used to generate results	Markov model. During the evaluation the model structure was interpreted as follows (based on the excel workbook as limited documentation was provided): • Year 0 to 5.25: ExteNET trial iDFS and OS data for the HR+ subgroup of the ITT population for the neratinib and placebo treatment arms were applied for the first 5.25 years (62 months) and extrapolated. • Year 5.25 to 8.5 years: HERA trial iDFS and OS data (comparing trastuzumab and placebo, Cameron et al., 2017) for the one year trastuzumab arm were extrapolated and applied to both neratinib and placebo for the following 3.3 years (up to 102.1 months). An adjustment of 15.3 months was applied to the time scale of the HERA trial data to align with the ExteNET trial (11 months' mean duration on trastuzumab therapy and 4.3 months' mean duration since trastuzumab). • 8.5 years+: UK General Population survival data were extrapolated and applied to estimate iDFS in both treatment arms thereafter. • It was assumed that the iDFS and OS treatment effect tapers to a HR = 1 between 5.25 years and 15.25 years.
Health states	Disease free, local recurrence, distant recurrence, death.
Cycle length	One month. Monthly cycles are reasonable in the model.
Transition probabilities	A Gompertz function fitted to iDFS and OS Kaplan-Meier data from the ExteNET trial was used up to and including cycle 62 (5.25 years). It may be more appropriate to use Kaplan-Meier data directly until a time point where the data is no longer reliable. The choice of the fitted Gompertz function is questionable considering the flexible Weibull (1 knot) had the better AIC and BIC. Additionally, the clinical plausibility of the tested functions could not be determined based on the information provided. iDFS post the trial period was estimated from long-term follow-up data (median follow up 11 years) from the HERA trial (1 year trastuzumab arm). This was applied from cycle 63 until and including cycle 102. The choice of the fitted Gompertz function is reasonable. However, this deviates from the typical approach of extrapolating only the clinical trial data presented (i.e. the ExteNET trial). This may be reasonable, however, sensitivity analysis was unable to be conducted to explore this assumption due to limitations in the model. UK general population survival data was used to extrapolate from cycle 103 until the end of the model. The use of UK mortality data is inappropriate for the Australian setting, but the direction and magnitude of resultant bias is uncertain. Note that this overall approach deviates from the typical approach of extrapolating only the clinical trial data presented (i.e. the ExteNET trial). Introduction of multiple data sources may be reasonable, however sensitivity analysis was not conducted to explore this assumption. It appears (based on the Section3_ExtrapolationModelling PowerPoint) validation was conducted by a visual comparison of the survival curve with that from Brenner (2004). Brenner (2004) was based on a

[8] PBAC (2006) Public summary document: Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin

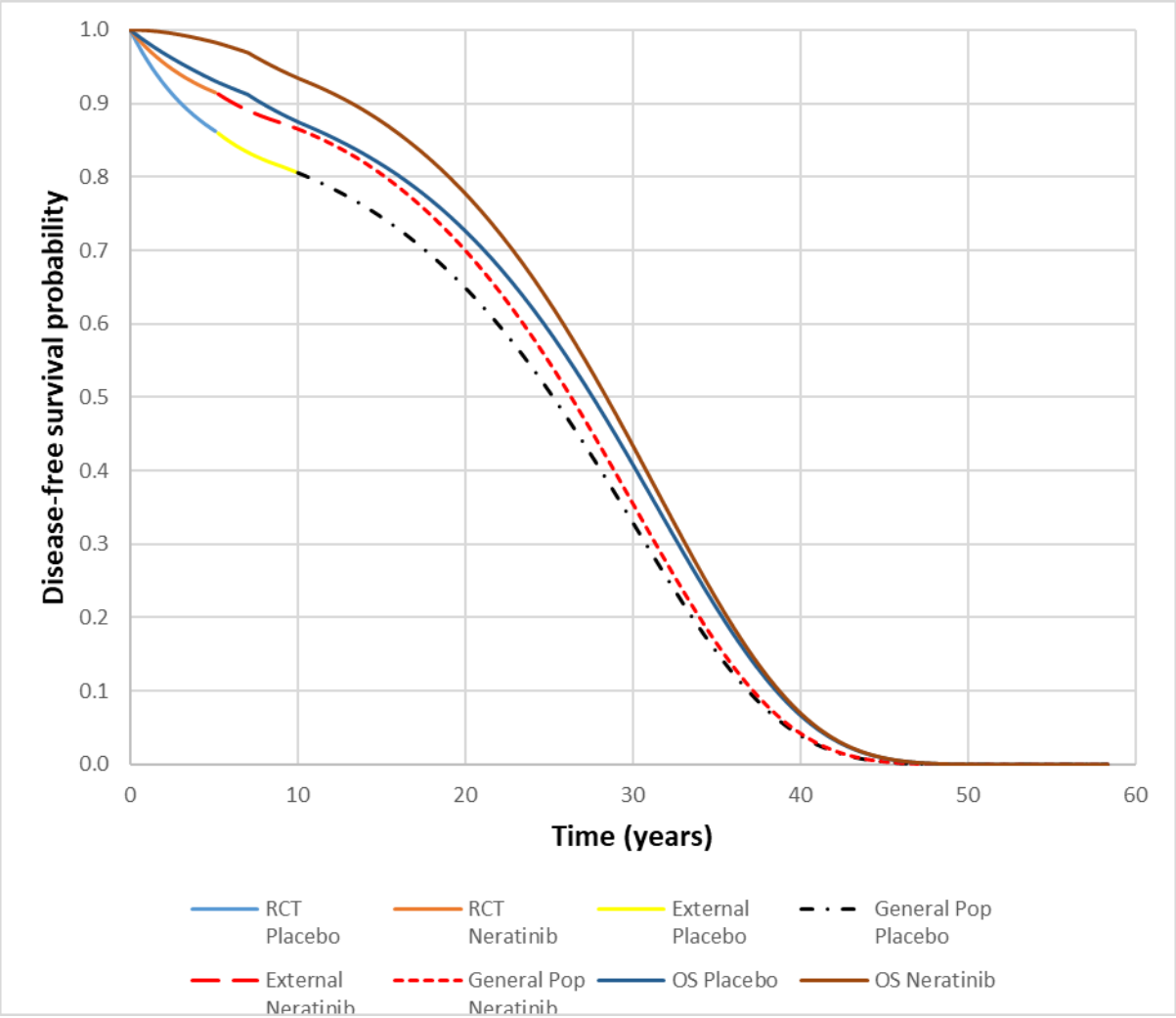
Component	Description
	survival analysis using old data. This validation is inappropriate as it does not consider recent advances with HER2 therapies. It was assumed that the iDFS and OS treatment effect tapered gradually until a HR of 1 occurred 10 years from the end of the ExteNET data (PSCR, p4). The PBAC has previously recommended that the treatment effect for adjuvant trastuzumab in eBC should be null after year 5, which is approximately ten years earlier than is currently assumed in the neratinib model.[9] The model assumed that recurrence is split 28% local vs 72% distant, and that this is the same between arms. This was based on the total population of the ExteNET trial.
Utilities	Garrison (2007), who cited Oestreicher 2005 and Hornberger (2002). EQ-5D results from the ExteNet trial in the iDFS health state may be a more appropriate source. The methods and utilities for local and distant recurrence could not be verified.
Disutilities	Lloyd (2006) for disutility of diarrhoea. The submission assumed that Grade ≥3 diarrhoea was associated with twice the utility of grade ≤2 diarrhoea. Brown (2013) (presumably from Nafees (2008)) for disutilities of vomiting, nausea and fatigue. Disutilities for adverse events other than diarrhoea were not applied in the model, despite presenting them in the submission.
Software package	Excel 2016

eBC: early breast cancer; iDFS: invasive disease free survival; HER2: human epidermal growth factor receptor 2; HR+: hormone receptor positive: HR: hazard rate ratio; ITT: intent to treat; OS: overall survival; PBAC: pharmaceutical benefits advisory committee; UK: United Kingdom
Source: Table 45, p101 of the submission

6.44 Figure 5 presents a visual representation of the extrapolation methods used in the submission.

[9] PBAC (2006) Public summary document: Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin

Figure 5: Extrapolated disease-free survival (DFS) and overall survival (OS) used in the base case.



Source: Figure 35, p109 of the submission.

6.45 The key drivers of the model and results are presented in Tables 10 and 11, respectively.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Time horizon	The 55 year time horizon is long compared to the 5 year follow-up period of the ExteNET trial.	High, favours neratinib
Extrapolation	Treatment effect continued beyond 5 year ExteNET follow-up period, tapering to a HR=1 10 years post follow-up.	Moderate, favours neratinib
Population	HR+ population rather than ITT from ExteNET trial	Moderate, favours neratinib
Dosage/wastage	214 mg daily for 8.23 months rather than 240mg daily and 9.37 scripts per patient used to estimate the financial impact.	Moderate, favours neratinib
Choice of extrapolation functions	Only selected functions were able to be tested in the model.	Unclear. Unable to conduct sensitivity analysis.
Extrapolated data sources	Extrapolation using multiple data sources rather than only the ExteNET trial without the application of external data. This may be reasonable, however sensitivity analysis was unable to be conducted on this assumption due to limitations in the model.	Unclear. Unable to conduct sensitivity analysis.
Application of mortality data	UK mortality data rather than Australian data.	Unclear. Unable to conduct sensitivity analysis. The ESC considered that this would have minimal impact in the ICER.
Application of utilities	From the literature rather than using utility weights for iDFS from the ExteNET trial.	Unclear. Unable to conduct sensitivity analysis as trial-based utilities were not provided.

iDFS: invasive disease free survival; HR+: hormone receptor positive: HR: hazard rate ratio; ITT: intent to treat; UK: United Kingdom
Source: Compiled during the evaluation.

Table 11: Results of the economic evaluation

Step and component	Neratinib	Placebo	Increment
Number of cases of recurrence or death at 5 years (from a cohort of 1000 patients, at cycle 60)*	84.31 (8.4%)	136.56 (13.7%)	-52.25 (-5.2%)
Costs (per patient)	$[redacted]	$[redacted]	$[redacted]
LYs (per patient)	14.66	13.89	0.78
QALYs (per patient)	12.84	12.14	0.70
Incremental cost/extra LY gained			$[redacted]
Incremental cost/extra QALY gained			$[redacted]

LY: life year; QALY: quality adjusted life year
Source: Table 54, p118 of the submission.
* Calculated during the evaluation

Methods used to generate results:

6.46 The submission provided insufficient detail to enable the economic model to be adequately evaluated. During the evaluation, several assumptions regarding the methodology and inputs had to be made based on the Excel workbook and accompanying PowerPoint presentation. The ESC noted that documentation supplied by submission, in particular the detail on model assumptions, was inadequate to allow sufficient understanding of the model, or allow confidence in its results.

6.47 OS data were not presented in the submission and it was claimed that it will not be available until late 2019. However, OS data for the ITT population were included in the economic model. The PSCR claimed that OS data were not used in the economic model. However, the ESC disagreed with this assertion and considered the base case

appeared to include OS from the ExteNET trial and the proportion alive at each time point differed for OS and iDFS. The ESC noted that the base case of the model appeared to reference information from the OS-ExteNET sheet and that this can be altered from the OS & DFS sheet. Furthermore, a source from the OS-ExteNET sheet in cell D24 suggests that an analysis of OS in the ITT population was conducted in March 2017. The source could not be verified. The ESC also noted that the OS data from the ExteNET trial includes the ITT population and not the HR+ subset.

6.48 Three separate data sources (ExteNET trial, HERA trial, and UK general population data) informed iDFS and OS. iDFS in the post-trial period was estimated from long-term follow-up data (median follow up 11 years) from the HERA trial (1 year trastuzumab arm). The PSCR stated that data from the HERA trial was used in the extrapolation because of a longer follow up period in the HERA trial compared to the ExteNET trial thus reducing uncertainty. The ESC considered there is an increased level of uncertainty when combining data from different studies. Sensitivity analysis involving extrapolating only the clinical trial data was not conducted to explore the impact of this and the ESC considered that this would have been informative.

Transition probabilities:

6.49 Although not clear in the submission, the PSCR stated that the iDFS data from the ExteNET trial were applied directly for 5.25 years with extrapolation occurring after this time point. In the ExteNET trial at 60 months after randomisation 91.2% of HR+ patients in the neratinib arm and 86.8% of patients in the placebo arm had not progressed. At cycle 60 in the economic model (using base case assumptions), iDFS was 92% in the neratinib arm and 86% in the placebo arm. Thus the difference in iDFS at 60 months was larger in the model (6%) compared with the observed data (4.4%). The ESC considered that using observed data would likely result in an increased ICER but this was difficult to quantify.

6.50 The iDFS and OS treatment effect tapered to a HR of 1 between 5.25 years and 15.25 years. The ESC noted that in its consideration of pertuzumab in 2006 the PBAC considered it reasonable to assume null effect after 5 years (Public Summary Document (PSD), July 2006 PBAC meeting, Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin) which was 3 years beyond the trial follow-up, in comparison with 10 years beyond the trial follow-up in this submission. The ESC noted that for pertuzumab in eBC the PBAC considered that the treatment effect may endure beyond five years, but there was uncertainty around the duration of benefit (PSD, July 2018 PBAC meeting, item 6.10 pertuzumab, paragraph 6.44). The ESC agreed with the evaluation that the duration of treatment effect is highly uncertain and although the 2 and 5 year follow up data showed a significant improvement in iDFS, the ESC considered this to be a small result in absolute terms and questioned how this was applied in the model.

6.51 The base case applied a Gompertz function to extrapolate the data despite the AIC and BIC results suggesting there were better fitting functions. The clinical plausibility and the best visually fitting extrapolation functions were unable to be verified from

the images provided in the submission due to them not being included in the electronic model and their small size in the accompanying slides. The AIC and BIC results, and the shape and scale parameters were unable to be verified as the statistical (R) output was not provided with the submission.

Utilities:

6.52 The submission applied utility estimates from the literature rather than applying the utility estimates from the ExteNET trial for the iDFS health state. The impact of this on the model results is unknown due to a lack of sensitivity analysis. The utility estimates used in the base case could not be verified due to the original sources not being cited in the references used in the submission. The PSCR argued utility values were not collected after recurrence and minimal data were available for patients with a recurrence (11 patients had utility data after recurrence). Therefore, utility values for each of the health states in the model could not be derived from the ExteNET data. There was no statistically significant difference observed in baseline utilities between the neratinib and placebo treatment groups (mean [95% CI], 0.855 [0.840-0.869]; 0.863 [0.850-0.876]). These values are similar to the utility value for the disease-free health state in the model (0.9; Garrison et al., 2007).

6.53 Utility estimates for the local recurrence and distant recurrence health states were identical. There are likely to be differences in symptoms associated with the location of the metastases in the distant recurrence health state (e.g. bone pain).

6.54 Disutilities were only applied for diarrhoea, and the duration they were applied for was shorter for neratinib than for placebo for Grade ≤ 2 diarrhoea (neratinib 0.1 weeks vs placebo 0.3 weeks).

Other issues:

6.55 Other issues with the model that were identified during the evaluation were:

- The time horizon in the base case (55 years) was long relative to the five year follow-up period of the ExteNET trial. The ESC noted that a 55 year time horizon is clinically implausible, however, the ICER was not sensitive to the time horizon unless shorter than 30 years (Table 14).
- 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.
- The use of loperamide after the initial 55 days of prophylaxis appears to be underestimated.
- Several treatments and the PBS codes used for the treatments for local and distant recurrence were inappropriate.
- The costs of endocrine therapies were not included in the model, despite 93.4% of patients in the ExteNET trial using concomitant endocrine therapy. The cost of these therapies would increase if patients spend longer in the iDFS health state.

- The cost of an ISH test was applied to all patients who enter the local recurrence health state, despite patients having received the test prior to initial trastuzumab treatment (i.e. prior to neratinib therapy).
- Several medical service/diagnostic costs were missing from the model, such as CT scans, blood tests etc. The PBAC noted that the ExteNET trial included monthly blood tests to monitor the impact of diarrhoea on patients and considered that patients treated with neratinib would require additional tests due to its toxicity.
- Several treatments for adverse events were inappropriate, such as the use of fentanyl for breakthrough pain when no therapy for baseline pain relief was proposed. Also the use of fentanyl and ondansetron do not align with their PBS restrictions.
- Drug wastage was not included and costs were based on a cost per tablet. The PSCR included wastage in the univariate sensitivity analyses and stated that neratinib is cost-effective when wastage was included in the economic model, however the ICER increased to $45,000 - $75,000 per QALY.

6.56 The ESC noted that the main cost driver was the cost of neratinib, but some offsets were also included for delayed recurrence. The PBAC noted that the neratinib cost per patient in the model appeared to be too low. This is because 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 accounts for discontinuation of patients who have progressed. When corrected, the drug cost per patient per month increased to $ less than $10 million, which increased the ICER to $45,000/QALY -$75,000/QALY. The drug cost and ICER would increase further if wastage is included.

6.57 Table 12 presents the sensitivity analyses presented by the submission.

Table 12: Sensitivity analyses presented by the submission

Variable	Base Case	Lower bound	Upper bound	ICER range
Discount rate: Outcomes	0.05	0.00	0.10	$[redacted]-$[redacted]
Discount rate: Costs	0.05	0.00	0.10	$[redacted]-$[redacted]
Disease-free utility	0.90	0.81	0.99	$[redacted]-$[redacted]
Mean age (years)	52.29	47.06	57.52	$[redacted]-$[redacted]
Local Recurrence annual cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]-$[redacted]
Distant recurrence annual cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]-$[redacted]
Loperamide prophylaxis cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]-$[redacted]
Cost per follow-up visit: Breast cancer clinic	$[redacted]	$[redacted]	$[redacted]	$[redacted]-$[redacted]
AE costs: Diarrhoea grade ≥3	$[redacted]	$[redacted]	$[redacted]	$[redacted]-$[redacted]
AE incidence: Diarrhoea grade ≥3 neratinib with prophylaxis	31%	28%	34%	$[redacted]-$[redacted]
Number of AEs experienced: Diarrhoea grade ≥3	1.00	0.90	1.10	$[redacted]-$[redacted]
AE utility decrements: Diarrhoea grade ≥3	-0.10	-0.09	-0.11	$[redacted]-$[redacted]
AE utility duration: Diarrhoea grade ≥3 Neratinib (weeks)	0.29	0.26	0.31	$[redacted]-$[redacted]
AE incidence: ALT increase grade ≥3 Neratinib	1.3%	1.2%	1.4%	$[redacted]-$[redacted]
Number of AEs experienced: ALT increase grade ≥3 Neratinib	1.00	0.90	1.10	$[redacted]-$[redacted]

ICER: incremental cost-effectiveness ratio; AE: adverse event; ALT: alanine aminotransferase

Sources: Figure 37, p119 of the submission; OWSA calcs sheet of the Nerlynx_PBAC_Section3_Nov2018 workbook.

6.58 Table 13 presents the key sensitivity analyses conducted during the evaluation. Table 14 presents sensitivity analyses around the time horizon.

6.59 The base case ICER presented in the submission was $45,000/QALY - $75,000/QALY. The ESC noted the ICER was sensitive to the following:

- using the HR+ group rather than the overall population. When the overall population is used the ICER increased to $45,000/QALY - $75,000/QALY. The ESC noted it was unclear whether the difference in risk between HR+ and HR- patients was plausible.
- assuming ongoing effect beyond trial follow-up. Where there is no treatment effect after trial follow-up the ICER increased to $45,000/QALY - $75,000/QALY. This analysis assumed a HR of 1 after 5 years rather than assuming the same survival for both treatment groups beyond the trial follow-up.
- using the recommended daily dose (240mg) rather than the dispensed trial average dose (214.3mg) increased the ICER to $45,000/QALY - $75,000/QALY. The ESC noted that it was unclear what the likely dosing would be in clinical practice.

Table 13: Summary of sensitivity analysis results

Analyses	Incremental cost	Incremental LYs	Incremental QALYs	ICER ($/LY)	ICER ($/QALY)
Base case	**$**	**0.78**	**0.70**	**$**	**$**
Univariate					
Population (base case HR+) Overall population	$	0.61	0.55	$	$
Age of cohort (base case 52.3 years) Mean age at diagnosis in Australia (60 years)	$	0.7	0.63	$	$
Treatment effect (base case taper to HR=1 at 15.25 years after ExteNET trial follow-up) Assume no treatment effect after trial follow-up	$	0.67	0.60	$	$
Dose per day (base case 214.3mg) 240mg (recommended dose)	$	0.78	0.70	$	$
Extrapolation (base case Gompertz applied to both ExteNET trial and external study data) Flexible Weibull (1 knot) to ExteNET trial data and Gompertz to external study*	$	0.80	0.72	$	$
Flexible Weibull (2 knots) to ExteNET trial data and Gompertz to external study data	$	0.63	0.57	$	$
Utilities (base case Garrison 2007) Earle (2000) Hall (2011) Lloyd (2006) (iDFS: 0.72; local and distant recurrence: 0.45)	$ $ $	0.78 0.78 0.78	0.76 0.61 0.56	$ $ $	$ $ $
Multivariate					
No wastage (240mg per day) and 9.37 scripts per patient (base case 214.3mg per day for 8.23 months) To match Section 4	$	0.78	0.70	$	$

LY: life year; QALY: quality adjusted life years; ICER: incremental cost-effectiveness ratio; HR+: hormone receptor positive; HR: hazard rate; iDFS: invasive disease free survival

Source: Compiled during the evaluation

Table 14: Sensitivity of ICER to time horizon.

Time Horizon (years)	Total Cost		Life Years		QALYs		ICER	
	Neratinib	Placebo	Neratinib	Placebo	Neratinib	Placebo	Per LY gained	Per QALY gained
5	$	$	4.50	4.36	3.99	3.87	$	$
10	$	$	7.92	7.57	6.99	6.68	$	$
15	$	$	10.44	9.93	9.20	8.74	$	$
20	$	$	12.25	11.62	10.78	10.22	$	$
25	$	$	13.46	12.76	11.83	11.19	$	$
30	$	$	14.18	13.43	12.44	11.77	$	$
35	$	$	14.53	13.76	12.73	12.04	$	$
40	$	$	14.64	13.87	12.83	12.13	$	$
45	$	$	14.66	13.89	12.84	12.14	$	$
50	$	$	14.66	13.89	12.84	12.14	$	$
55 (base case)	$	$	14.66	13.89	12.84	12.14	$	$

Source: Created during the evaluation from altering the time horizon in Nerlynx_PBAC_Section3_Nov2018
QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; LY: life year

6.60 Table 15 presents the additional sensitivity analysis for the inclusion of ExteNET trial utility values for iDFS . The PSCR stated that the iDFS utility value from the ExteNET trial was 0.855 (95% CI: 0.840 0.869) for neratinib; and 0.863 (0.850 0.876) for placebo. The PSCR also provided utility values for those patients who experienced grade 3 diarrhoea (0.826) and those without experiencing diarrhoea (0.838 (95% CI: 0.809, 0.843)). The PSCR did not provide 95% CI's for patients who experienced grade 3 diarrhoea. The utility values provided for iDFS were unable to be verified. The ICER from the sensitivity analysis using the mean baseline utility value of 0.86 from the ExteNET trial was $45,000/QALY - $75,000/QALY. It is unclear whether this calculation included the PSCR's estimate for the disutility of diarrhoea. The ESC noted that applying the utility of 0.86 for the disease-free state while leaving the disutility for diarrhoea at 0.1 yielded an ICER of $45,000/QALY - $75,000/QALY.

Table 15: Sensitivity of ICER to trial utility values for invasive disease free state

	Neratinib	Placebo	Incremental	ICER
Base case				
Total cost ($)	$	$	$	
QALYs	12.84	12.14	0.70	**$ /QALY**
Utility values: ExteNET				
Total cost ($)	$	$	$	
QALYs	12.04	11.38	0.65	**$ /QALY**
Recalculated using utility of 0.86 for iDFS and leaving the disutility for diarrhoea at 0.1*				
Total cost ($)	$	$	$	
QALYs	12.31	11.64	0.67	**$ /QALY**

QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio
Source: Table 4, p6 of the PSCR
*calculated during the ESC evaluation

Drug cost/patient/course

6.61 The cost per patient per course (one year) was $[redacted]. This was based on the expected dose of 240 mg daily for 12 months. The cost per patient per course based on the trial data; from the model and from the financial estimates is shown in Table 16. As noted above, the PBAC considered that drug costs in the model appear to be too low. The PBAC also agreed with the DUSC that drug costs in the financial estimates appear to be too high.

Table 16: Drug cost per patient for neratinib

	Trial dose and duration	Model	Financial estimates
Mean dose	210.4 mg/day[a]	214.3 mg/day[b]	240 mg/day
Mean duration	8.23 months	8.23 months	9.37 months[c]
Total mg administered	54,194 mg[d]	*52,911 mg*[e]	*67,464 mg*[e]
Cost/patient/month	$[redacted][f]	$[redacted][f]	$[redacted][f]
Cost/patient/course	$[redacted][g]	$[redacted] model $[redacted] corrected[h,i] $[redacted] incl. wastage[j]	$[redacted]

Source: Table 26, pp 156-157 of the trial report, Nerlynx_PBAC_Section3_Nov2018 workbook, sheet 3a of the Nerlynx_utilisation-and-cost-model_November2018. Italicised values have been calculated.

[a] actual dose intensity in the trial (actual cumulative dose divided by the treatment duration)

[b] prescribed dose intensity in the trial (cumulative prescribed dose during treatment period divided by treatment duration)

[c] assumes 27% (the proportion in the trial discontinuing due to AEs or recurrence) receive 2 months of treatment and the remainder receive 12 months, without accounting for dose reductions.

[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, without wastage

[j] assumes that tablets in the remainder of month are wasted, rather than a cost per tablet, without correction of drug cost calculations

Estimated PBS usage & financial implications

6.62 This submission was considered by DUSC.

6.63 Table 17 presents the estimated use and financial implications of listing neratinib.

Table 17: Estimated use and financial implications

	Year 1 2020	Year 2 2021	Year 3 2022	Year 4 2023	Year 5 2024	Year 6 2025
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						
Net cost to PBS/RPBS**	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS***	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] Assuming 9.37 scripts per patient as estimated by the submission.

* The reported number of patients treated was based on 50% of eligible grandfathered patients from a neratinib access program (total 150 patients in the program). Total had been amended to include all access program patients.

**The reported net cost does not include loperamide co-payments. Corrected net cost in italics.

***The reported cost of outpatient MBS services was calculated using 100% of the MBS fee. Corrections made with the 85% benefit in italics.

Source: Tables 63 and 64, p130 of the submission.

PBS: pharmaceutical benefits scheme; RPBS: repatriation schedule of pharmaceutical benefits; MBS: Medicare benefits schedule; DHS: department of human services.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be $60 to $100 million.

6.64 The submission nominated the market size and uptake rate as potential sources of uncertainty in the financial estimates. No sensitivity analyses of the financial impact were conducted.

6.65 The DUSC considered the submission's estimates of both patients electing treatment and patients completing 12 month treatment are likely to be overestimated. Table 18 shows the DUSC's revised utilisation estimates:

Table 18: Comparison of submission and DUSC revised estimates of patient numbers

	2020	2021	2022	2023	2024	2025
Submission estimates						
Patients initiating trastuzumab in previous year (PBS data, [redacted]% growth)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who complete trastuzumab therapy ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who are hormone receptor positive ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Patients electing treatment (60-80%)	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Patients electing treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients completing 12 months treatment ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DUSC estimates						
Patients initiating trastuzumab in previous year (DUSC data, 5% growth)	2,270	2,384	2,503	2,628	2,759	2,897
Patients who complete trastuzumab therapy ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who are hormone receptor positive ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Patients electing treatment (60%)	60%	60%	60%	60%	60%	60%
Patients electing treatment	**726**	**762**	**801**	**841**	**883**	**927**
Patients completing 12 months treatment ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Difference between submission and DUSC revised estimates						
Patients electing treatment	-[redacted]%	-[redacted]%	-[redacted]%	-[redacted]%	-[redacted]%	-[redacted]%
Patients completing 12 months treatment ([redacted]%)	-[redacted]%	-[redacted]%	-[redacted]%	-[redacted]%	-[redacted]%	-[redacted]%

Compiled during the DUSC evaluation

6.66 The DUSC revised estimates of patient numbers (both electing treatment and completing treatment) are substantially lower than the submission estimates. The main differences between the submission and the DUSC revised estimates are:

- The number of patients initiating trastuzumab in the previous year were taken from the DUSC report[10] (rather than imputed from prescription counts); which is a more reliable method.
- The DUSC considered that the submission uptake rates underestimated the severity of diarrhoea associated with neratinib and its impact on quality of life in a population of patients who have already been through complex treatment. The DUSC noted that the Sponsor's advisory board of 10 clinicians had estimated the uptake to be between 50% and 66%. The DUSC estimates assumed the uptake would be 60% across all estimate years, rather than 60-80% as assumed in the submission.
- Based on the ExteNET trial, the submission assumed that 28% of patients would discontinue treatment after 2 months due to adverse events. The submission then assumed that the remaining 72% would go on to complete 12 months treatment. DUSC considered that it was unrealistic to assume there would be no discontinuations between 2 and 12 months. This was also inconsistent with the

[10] Figure 10, Medicines for HER2 positive metastatic breast cancer, February 2018, http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/2018-02/medicines-for-her2-positive-metastatic-breast-cancer

estimated mean duration of treatment in the economic model. DUSC also noted that all cause discontinuation in the ExteNET trial for neratinib patients was 38.9% and so estimated that 61.1% of patients would complete PBS treatment (compared to the submission assumption of 72.5%).

6.67 The DUSC noted that dose reductions were not accounted for in the submission despite the submission reporting that 36.9% of patients in the ExteNET trial had dose reductions. DUSC considered that not accounting for these dose reductions would add to the overestimation of prescriptions and government costs. DUSC also considered that if the extent of dose reduction in clinical practice is greater than that observed in the trials that this may impact on the efficacy of neratinib.

6.68 More efficacious drugs are likely to affect uptake in the medium to longer term. DUSC considered that there is evidence that the near market competitor T-DM1 in the post-neoadjuvant setting is more effective than neratinib for both ER positive and negative patients. Thus if T-DM1 is listed on the PBS for this indication in the future, the uptake of neratinib would be greatly reduced. The pre-PBAC response noted the emergence of T-DM1 in breast cancer treatment but argued that T-DM1 would be used in a small percentage of patients and its impact on neratinib uptake would be minimal.

6.69 Other issues with the submission's estimated use and financial estimates as identified during evaluation were:

- The number of patients in Year 1 is underestimated. The submission calculated 50% of grandfathered patients would be eligible for PBS supply rather than applying this figure to the number of scripts dispensed directly as stated.
- Loperamide use may be underestimated in the submission. The financial estimates assumed that prophylaxis is only provided during the first 2 months of neratinib therapy. However, in the ExteNET trial treatment emergent diarrhoea of any grade was 42.4% in the twelfth month.
- No other treatments for adverse events were included as PBS listed medicines likely to be impacted by neratinib. This is inconsistent with several PBS listed medicines for the treatment of adverse events being included in the economic model.
- Later line treatments of eBC or metastatic breast cancer were not considered to be impacted by the listing of neratinib. It is likely that later line treatments will likely be impacted, including the use of other HER2 therapies.
- Several MBS items likely to be affected by the listing of neratinib were not included in the financial estimates.

Quality Use of Medicines

6.70 The submission provided details of the proposed Risk Management Plan (RMP) in Australia. However, no post-marketing surveillance studies or additional pharmacovigilance or risk minimisation activities beyond routine activities were specified in the RMP were proposed. The PBAC agreed with DUSC that given the substantial toxicity profile of neratinib, the QUM section of the submission was sparse and inadequate.

Financial Management – Risk Sharing Arrangements

6.71 The submission proposed an in principle risk sharing arrangement whereby a rebate of [redacted]% of the cost of neratinib would be paid for any usage beyond the eligible patient population (assuming 100% uptake). The DUSC and ESC noted that the RSA proposed in the submission was for [redacted]% rebate above the eligible population rather than the estimated population. The ESC considered that this would result in uncertainty as there is an inherent margin for error before the rebate is even applied.

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

7 PBAC Outcome

7.1 The PBAC did not recommend an Authority Required listing of neratinib for extended adjuvant treatment of patients with early-stage human epidermal growth factor receptor-2 positive (HER2+) overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy. The PBAC considered that the clinical place for neratinib is unclear given the shift toward treating high risk patients in the neoadjuvant setting, and the small and uncertain benefit of neratinib treatment which is balanced against the substantial risk of adverse events (AEs), in particular severe diarrhoea. The PBAC considered the economic analysis presented to be highly uncertain, and the uptake and financial estimates to be overestimated.

7.2 The PBAC noted the proposed PBS listing is narrower than the registered TGA indication and relied on a subgroup of the ExteNET trial. The proposed listing is for patients with HER2+, HR+, eBC who have completed their adjuvant trastuzumab treatment within the previous year. The PBAC considered that it may be appropriate to restrict use to HR+ patients given the greater improvement in iDFS in this subgroup, however the ExteNET trial was not powered to detect if HR status is a treatment effect modifier. The PBAC further noted the efficacy of neratinib in lower risk patients was uncertain, including those with stage 1 or node negative disease given these patients were excluded from ExteNET following protocol amendment 3.

7.3 The PBAC considered that the clinical place for neratinib is unclear given the move towards neoadjuvant chemotherapy in high risk patients and emerging treatments in the neoadjuvant and adjuvant settings. The PBAC noted that neoadjuvant chemotherapy allows assessment of response to therapy at the time of surgery and pathological complete response (pCR) has demonstrated prognostic importance. The PBAC also noted the recently published data from the KATHERINE trial demonstrating the efficacy of trastuzumab emtansine (T-DM1) in patients with residual invasive

disease after completing neoadjuvant therapy. The PBAC noted there are limited data assessing the efficacy of neratinib following T-DM1, or adjuvant trastuzumab plus pertuzumab. The PBAC further considered that a listing for neratinib should restrict use to following trastuzumab monotherapy, to be consistent with the available evidence.

7.4 The PBAC noted that input from three individuals, one health care professional and two organisations (BCNA and MOGA) was received in support of a PBS listing for neratinib.

7.5 The PBAC considered the nominated comparator of usual care/placebo was reasonable. 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.

7.6 The submission was based on one head-to-head randomised trial comparing neratinib to placebo (N=2,840): ExteNET trial. The PBAC noted the ESC's concerns around the high number of protocol amendments throughout the five year trial period and considered that the trial had a high risk of bias particularly due to the differential loss to follow-up associated with protocol amendments 9 and 13 which may have impacted on the frequency of events in each arm. The PBAC also noted that the trial was not powered to assess efficacy in the subgroup of patients for whom a listing is proposed and patients with node negative disease may be under represented.

7.7 The PBAC noted with a median follow-up of 5.3 years the difference in iDFS for the ITT population at 5 years was 2.5% (90.2% for neratinib versus 87.7% for placebo), with an overall reduction in risk of 27% (HR=0.73, 95% CI: 0.57, 0.92, p=0.004). The benefit in the HR+ subgroup was greater than that in the HR- subgroup (difference in iDFS at 4 years of 4.1%, HR=0.60 (95% CI: 0.43, 0.83) versus 0.6%, HR=0.95 (95% CI: 0.66, 1.35)), although the test for interaction across the subgroups was not statistically significant (p=0.063).

7.8 The PBAC also noted the subgroup analyses by nodal status, prior neoadjuvant therapy, stage at diagnosis and the time since completion of trastuzumab. Although not statistically significant, the point estimates for the HRs suggest a possible smaller benefit in node negative patients, stage 1 patients, and those who completed trastuzumab therapy more than one year prior.

7.9 The pre-PBAC response noted that for the patient population who were HR+ and randomised within 1 year from the end of their adjuvant trastuzumab therapy, the difference in iDFS at 2 years was 4.5%, with a HR of 0.49 (95% CI: 0.31, 0.75).

7.10 The PBAC noted the greater reduction in quality of life with neratinib than placebo, as measured using the EQ-5D and FACT-B instruments, within the first month after randomisation. The PBAC considered this is likely to be due to the onset of diarrhoea.

7.11 Overall, the PBAC considered the difference in iDFS to be small 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. Further, the PBAC noted without overall survival data the long term benefits of neratinib therapy are unknown.

7.12 The PBAC noted the incidence of diarrhoea (any grade) was higher with neratinib versus placebo (95.4% vs. 35.4%, respectively), as was the incidence of grade 3 or 4 diarrhoea (39.9% vs. 1.6%, respectively). Diarrhoea was the most common adverse event leading to study discontinuation, observed in 16.8% of patients in the neratinib arm. The PBAC considered that the AE data show 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.

7.13 Overall, the PBAC considered the adverse events experienced with neratinib therapy compared to placebo were significant and may outweigh the small benefit for some patients.

7.14 The submission presented a cost-utility analysis based on the ExteNET trial and a modelled evaluation. The PBAC noted that the documentation supplied by submission, in particular the detail on model assumptions, was inadequate to allow sufficient understanding of the model, or allow confidence in its results. The PBAC noted that extrapolation of the trial data and the use of external data sources resulted in uncertainty that could not be fully evaluated in sensitivity analyses.

7.15 The PBAC considered the base case ICER of $45,000/QALY - $75,000 gained to be high and uncertain, and likely underestimated due to assumptions which appeared to favour neratinib, including:

- Incorporating a substantial gain in OS despite no OS data from the ExteNET trial being presented in the submission (although it appeared to be included in the model);
- The relatively long time horizon for the base case (55 years) compared with five year follow-up for the ExteNET trial. The PBAC considered that a 40 years would be more appropriate, although noted that the ICER was not sensitive to the time horizon unless shorter than 30 years;
- The treatment effect was based on a subgroup of the ExteNET trial, and was assumed to continue beyond the 5 year ExteNET follow-up period, tapering to a HR of 1 at 10 years post follow-up. The PBAC considered that a treatment effect was assumed in the model for an unreasonably long duration;
- The model underestimated costs associated with neratinib treatment as the use of loperamide was underestimated, costs of endocrine therapies were not included, several medical service/diagnostic costs were not included, and drug wastage was not included in the base case; and

- The same utility value was used for recurrence states regardless of the location of metastases.

7.16 The PBAC noted the financial estimates were high and considered them to be uncertain. The PBAC considered the uptake was overestimated, particularly given the change in approach to treating high risk HER2+ patients, and that dose reductions with neratinib were not accounted for. The PBAC also noted the costs associated with treating drug toxicities and monitoring were underestimated.

7.17 The PBAC considered that any resubmission would need to be a major submission and would need to address the following issues:

- the clinical place and applicability of the trial evidence given the emerging therapies for the adjuvant treatment of breast cancer;
- adjuvant pertuzumab and T-DM1 as near market comparators;
- provide available OS data. The PBAC noted that OS data will be available late 2019;
- revise the economic model to address the issues outlined in Section 6;
- reduce the price such that the ICER is consistent with the previously recommended ICERs for other adjuvant breast cancer therapies; and
- revise the estimates of the financial implications to address the issues outlined in Section 6.

7.18 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 in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.