NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [ID981]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [ID981]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from **Pierre Fabre**

2. **Clarification questions and company responses**
   a) Further clarification request and response (Q. B10)

3. **Patient group, professional group and NHS organisation submission** from:
   a) Breast Cancer Now and Breast Cancer Care
   b) UK Breast Cancer Group

4. **Expert personal perspectives** from:
   a) Dr Ciara O'Brien, Consultant Medical Oncologist – clinical expert, nominated by UK Breast Cancer Group
   b) Melanie Sturtevant – patient expert, nominated by Breast Cancer Now
   c) Professor Nigel Bundred, Professor of Surgical Oncology – clinical expert, nominated by Pierre Fabre

5. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

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Post-technical engagement documents

7. **Technical engagement response from Pierre Fabre**
   a) Submission for updated PAS

8. **Technical engagement responses from experts:**
   a) Dr Ciara O'Brien, Consultant Medical Oncologist – clinical expert, nominated by UK Breast Cancer Group

9. **Technical engagement responses from consultees and commentators:**
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10. **Evidence Review Group critique of company response to technical engagement** prepared by KSR

11. Final Technical Report

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Neratinib (NERLYNX®) for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab [ID981]

Document B

Company evidence submission

Submitted by Puma Biotechnology

3 April 2019

File name	Version	Contains confidential information	Date
ID981_Neratinib in eBC_DocB_03April2019_redacted	2	NO	03 April 2019

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

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Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

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Tables and figures

Abbreviations

AAT	anthracycline-containing adjuvant trastuzumab
ABACUS	Awareness and Beliefs About Cancer
AE	adverse event
AIC	Akaike information criterion
Akt/PKB	Akt/protein kinase-B
ANCOVA	analysis of covariance
AR	adverse reaction
ATP	adenosine triphosphate
AUD	Australian dollar
BCIRG	Breast Cancer International Research Group
BIC	Bayesian information criterion
bid	twice daily
BNF	British National Formulary
CAD	Canadian dollar
CASP	Critical Appraisal Skills Programme
CI	confidence interval
CNS	central nervous system
CRF	case report form
CT	computed tomography
DCIS	ductal carcinoma in situ
DDFS	distant disease-free survival
DFS	disease-free survival
DFS-DCIS	disease-free survival including ductal carcinoma in situ
DSU	Decision Support Unit
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
eMIT	Electronic Market Information Tool
EOT	end of treatment
ER	oestrogen receptor
ERG	Evidence Review Group
ERK	extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
ESMO-MCBS	European Society for Medical Oncology Magnitude of Clinical Benefit Scale
ExteNET	Extended Adjuvant Treatment of Breast Cancer With Neratinib
FACT-B	Functional Assessment of Cancer Therapy–Breast
FinHer	Finland Herceptin trial
FISH	fluorescence in situ hybridisation
GI	gastrointestinal
GP	general practitioner
HER2	human epidermal growth factor receptor 2

HERA	HERceptin Adjuvant
HR	hormone receptor
HR−	hormone receptor-negative (oestrogen receptor-negative and progesterone receptor-negative)
HR+	hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive)
HRQoL	health-related quality of life
HTA	health technology assessment
IBCSG	International Breast Cancer Study Group
IBS	Integrated Brier score
IC_{50}	half maximal inhibitory concentration
ICER	incremental cost-effectiveness ratio
iDFS	invasive disease-free survival
IHC	immunohistochemistry
IP	investigational product
IQR	interquartile range
ITT	intention to treat
IV	intravenous
LVEF	left ventricular ejection fraction
LY	life-year
LYG	life-year gained
MA	marketing authorisation
MAPK	mitogen-activated protein kinase
MUGA	multigated acquisition
NA	not applicable
NAT	non-anthracycline adjuvant trastuzumab
NCCTG	North Central Cancer Treatment Group
NCI-CTC	National Cancer Institute *Common Terminology Criteria*
NCI-CTCAE	National Cancer Institute *Common Terminology Criteria for Adverse Events*
NE	not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	not reported
NSABP	National Surgical Adjuvant Breast and Bowel Project
NT	no treatment
NYHA	New York Heart Association
OS	overall survival
OTC	over the counter
pCR	pathological complete response
PDRS	postdistant recurrence survival
PI3K	phosphatidyl-inositol-3-kinase
PR	progesterone receptor
PRO	patient-reported outcome
q4h	every 4 hours

q6-8h	every 6-8 hours
QALY	quality-adjusted life-year
qd	once daily
QoL	quality of life
RCT	randomised controlled trial
SABCS	San Antonio Breast Cancer Symposium
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SLR	systematic literature review
SMC	Scottish Medicines Consortium
SmPC	summary of product characteristics
STA	single technology appraisal
TA	technology appraisal
TCH	docetaxel + carboplatin + trastuzumab
TEAE	treatment-emergent adverse event
THB	Thai Baht
tid	three times a day
TNM	tumour-node-metastasis
TTDR	time to distant recurrence
UK	United Kingdom
US	United States

B.1 Decision problem, description of the technology, and clinical care pathway

B.1.1 Decision problem

This submission covers neratinib's full marketing authorisation for this indication: the extended adjuvant treatment of adult patients with early-stage hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-overexpressed/amplified breast cancer and who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy (Table 1).[1]

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Patients with early HR+, HER2+ breast cancer who have completed a course of adjuvant trastuzumab less than 1 year ago.	As per the scope. The ITT population and safety population of the ExteNET and CONTROL trials will also be included in the evidence submission for completeness, which included all patients with HER2+ breast cancer regardless of HR status or time from completion of trastuzumab-based therapy. Early-stage breast cancer in the neratinib clinical trials included patients with stage I-III tumours.	The primary evidence supporting the submission does not differ from the NICE scope. For completeness, the ITT and safety populations of the neratinib clinical trials will provide supplementary efficacy and safety data from all participants who received neratinib.
Intervention	Neratinib		NA
Comparator(s)	Standard treatment with no further HER2-directed therapy	As per the scope: no treatment, represented by the placebo arm of the ExteNET trial	No treatment is consistent with the NICE scope, see Sections B.1.3.6 and B.3.2.3
Outcomes	▪ OS ▪ DFS ▪ Adverse effects of treatment ▪ Health-related quality of life	As per the scope, including: ▪ iDFS (2 years and 5 years) ▪ DFS-DCIS ▪ Distant DFS ▪ Cumulative incidence of CNS recurrence ▪ TTDR ▪ Adverse effects of treatment ▪ Health-related quality of life	DFS includes iDFS, DFS-DCIS, and distant DFS, which were all outcomes in ExteNET. iDFS is the primary outcome of ExteNET; DFS-DCIS, distant DFS, CNS recurrence, and TTDR were secondary outcomes in ExteNET. OS data from ExteNET in the HR+ subset is not expected during the appraisal period. This is an event-driven endpoint; while data for the ITT population will read out by [redacted], data for the HR+ subset will only be available from [redacted], and the sponsor/Puma remains blinded until then.
Subgroups to be considered	None identified	Subgroups of the ExteNET trial population provide the primary data; no further subgroups within this population are considered.	NA
Special considerations, including issues related to equity or equality	No special considerations, including issues related to equity or equality, were identified. Neratinib is not considered by the company to meet NICE End of Life criteria.		

Abbreviations: CNS, central nervous system; DFS, disease-free survival; DFS-DCIS, disease-free survival including ductal carcinoma in situ; HER2+, human epidermal growth factor receptor 2-positive; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; ITT, intention to treat; NA, not applicable; OS, overall survival; PAS, patient access scheme; TTDR, time to distant recurrence.

B.1.2 Description of the technology being appraised

A product description of neratinib is presented in Table 2 and detailed in the following subsections. In addition, the following documents are included in Appendix C in support of this appraisal:

- The Summary of Product Characteristics (SmPC)
- The European public assessment report produced by the regulatory authorities

Table 2. Technology being appraised

UK approved name (brand name)	Neratinib (NERLYNX®)
Mechanism of action	Neratinib is a potent, irreversible pan-ErbB tyrosine kinase inhibitor that blocks mitogenic growth factor signal transduction through covalent, high-affinity binding to the ATP-binding site of 3 EGFRs—EGFR (encoded by ErbB-1), HER2 (encoded by ErbB-2), and HER4 (encoded by ErbB-4)—or their active heterodimers with HER3 (encoded by ErbB-3). This results in sustained inhibition of these growth-promoting pathways with HER2-positive or HER2-mutant (HER2+) breast cancers. Neratinib inhibits kinase activity through intracellular irreversible binding at a targeted cysteine residue in the ATP-binding pocket of these receptors. Neratinib irreversibly binds to HER1/HER2 and HER4 receptors and reduces EGFR and HER2 autophosphorylation and downstream MAPK (originally called ERK) and Akt/PKB signalling pathways. Neratinib potently inhibits tumour cell proliferation in vitro, with anti-tumour activity in EGFR- and/or HER2-expressing carcinoma cell lines with a cellular IC_{50} < 100 nM.[2,3] Neratinib has activity in HER2+ breast cancer cell lines that are both HR+ and HR–[4]; however, bidirectional cross talk between HR and HER2 signalling pathways may explain the notable efficacy of neratinib in HR+/HER2+ tumours. HER2 activation is recognised as a mediator of endocrine resistance, but inhibition of HER2 can reactivate ER signalling. Increased ER signalling can then provide an escape mechanism causing development of resistance to HER2-directed treatment. Simultaneous blockade of both ER and HER2 signalling pathways in HR+/HER2+ breast cancer may result in enhanced and sustained anti-tumour activity, as extended ErbB blockage may re-sensitise the ER signalling pathway to endocrine therapy.[5,6]
Marketing authorisation	Marketing authorisation was granted by the European Commission on 31 August 2018.
Indications and any restriction(s) as described in the SmPC	Neratinib is indicated for the extended adjuvant treatment of adults with early-stage HR+, HER2-overexpressed/amplified breast cancer and who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy.
Method of administration and dosage	Neratinib is administered orally. The recommended dose is 240 mg neratinib, administered as 6 × 40 mg tablets taken once daily and continually for 1 year. Neratinib should be taken with food, preferably in the morning.
Additional tests or investigations	The indicated population is people with HR+/HER2+ breast cancer who have completed a course of trastuzumab; however, as receptor and gene testing will already have been completed before initiating trastuzumab, no additional testing of receptor status is anticipated to be required to start neratinib therapy.

List price and average cost of a course of treatment	List price: £4,500 per 180 tablets. European licensing of neratinib for early breast cancer has been transferred to Pierre Fabre: confirmation of final list price with the Department of Health is pending. Average cost of course of treatment: [redacted]
Patient access scheme (if applicable)	Discussions with NHS England are pending at the time of submission.

Abbreviations: Akt/PKB, Akt/protein kinase-B; ATP, adenosine triphosphate; EGFR, epidermal growth factor receptor; ER, oestrogen receptor; ERK, extracellular signal-regulated kinase; HER, human epidermal growth factor receptor; HR, hormone receptor; IC_{50}, half maximal inhibitory concentration; MAPK, mitogen-activated protein kinase; PAS, patient access scheme; SmPC, summary of product characteristics.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease background: early HR+/HER2+ breast cancer

Breast cancer is a malignant tumour that starts in the breast tissue.[7] Molecular subtypes of breast cancer are distinguished by biomarkers that drive tumour growth, such as HRs and excess levels of human epidermal growth factor receptor-2 (HER2), which affect breast cancer prognosis and treatment decisions.[8] Specific HRs of interest include oestrogen receptors (ERs) and progesterone receptors (PRs), which induce breast tissue growth or change in response to changing levels of these female hormones.[9] Overexpression of the HER2 oncogene (HER2 positivity, or HER2+) has been shown to be a dominant driver of breast cancer tumours.[10] HER2 increases tumour cell metabolic functions, supports cell survival, induces proliferation and increases invasiveness.[11] Table 3 summarises the main breast tumour subtypes based on HR and HER2 status.

Table 3. Breast tumour subtypes based on HR and HER2 status

Biomarkers	Description
HR+ /HER2−	Best prognosis, given that tumours are generally responsive to hormonal therapy, slow growing, and less aggressive than other subtypes.
HR+/HER2+	HR+/HER2+ cancers tend to be more aggressive than HR+/HER2− cancers and are highly positive for HER2 or Ki67 (indicator of a large proportion of actively dividing cells).
HR−/HER2+	Poorer short-term prognosis compared with HR+ breast cancers; tend to grow and spread more aggressively than other breast cancers.
HR−/HER2−	Poorer short-term prognosis than other breast cancer types, as there are no targeted therapies for these tumours. Proportionally more common in black women than white women, in those with *BRCA1* gene mutation versus non-*BRCA1*, and in premenopausal vs. postmenopausal women.

Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HR+, hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive); HR−, hormone receptor-negative (oestrogen receptor-negative and progesterone receptor-negative).

Adapted from ACS (2015)[8]; Dai et al. (2016)[12]; Trop et al. (2014)[13]

People with HR+/HER2+ breast cancer have tumours that coexpress HRs (ER and/or PR) and HER2. This coexpression modulates tumour response to both HER2-directed therapy and hormonal (endocrine) therapy, as a result of bidirectional signalling, or 'cross talk' between the ER and HER2 signalling pathways. Bidirectional cross talk is a potential mechanism of action of endocrine resistance that may be implicated in the development of resistance to HER2-directed agents and disease recurrence.[5,6] ER signalling appears to be a major compensatory pathway driving the progression of HR+/HER2+ breast cancers treated with HER2 inhibitors.[5] HER2 activation is recognised as a mediator of endocrine resistance, but inhibition of HER2 can reactivate ER signalling. Increased ER signalling can then provide an escape mechanism causing development of resistance to HER2-directed treatment. In this way, simultaneous blockade of both ER and HER2 signalling pathways in HR+/HER2+ breast cancer may result in enhanced and sustained anti-tumour activity, as extended ErbB blockage may re-sensitise the ER signalling pathway to endocrine therapy.[5,6]

B.1.3.2 Breast cancer staging

At diagnosis, in addition to molecular subtyping, breast cancer is classified into stages according to the extent and spread of the disease. Early breast cancer can be classed as non-invasive or invasive.[8] There are two types of non-invasive breast cancer: ductal carcinoma in situ (DCIS) and lobular carcinoma in situ. DCIS is the earliest form of breast cancer and occurs when abnormal cells replace the normal epithelial cells of the breast ducts. Lobular carcinoma in situ occurs when cells that look like cancer cells grow in the lobules of the breast. Invasive breast cancer occurs when the cancer cells have spread through the walls of the glands or ducts into the surrounding tissue.[8]

The American Joint Committee on Cancer[8,14] and the Union for International Cancer Control[15] use the internationally recognised tumour-node-metastasis (TNM) staging system, which assesses tumour size (T), lymph node involvement (N), and presence of metastases (M). Stage 0 is non-invasive DCIS. Stages I to III describe invasive breast cancer that has spread locally to the breast tissue and possibly the lymph nodes in the armpit (node positive). Stage IV is advanced metastatic disease that has spread from the breast to other parts of the body.

Survival for breast cancer is strongly related to the stage of the disease at diagnosis. One-year net survival for breast cancer is highest for patients diagnosed at stage I, and lowest for those diagnosed at stage IV: 100% of patients diagnosed at stage I survived their disease for at least 1 year compared with only 63% of those diagnosed at stage IV.[16] However, the Herceptin Adjuvant (HERA) study shows approximately 24% of those with early HER2+/HR+ breast cancer still experience a local, regional,

or distant metastatic recurrence or die within 10 years despite treatment.[17] Metastatic breast cancer has a poor prognosis: the 5-year survival rate for metastatic breast cancer in England is 15%.[18,19]

B.1.3.3 Epidemiology of early HR+/HER2 breast cancer

In the UK, breast cancer is the most common cancer in women, with approximately 45,960 people diagnosed with breast cancer in England in 2016.[20] Most breast cancer cases in the UK are diagnosed at an early stage, which has led to a decrease in mortality rates in recent decades.[21] In 2010-2011, approximately two-thirds of women (65%) diagnosed with breast cancer in England and Wales had survived their disease for 20 years or more. However, UK mortality rates from breast cancer are the 14th highest in Europe. Breast cancer is the second most common cause of cancer death in women in the UK, with approximately 9,685 deaths from breast cancer in England per year.[20,22]

Approximately 15% to 25% of all invasive breast cancer tumours are HER2+; of HER2+ breast cancers, approximately 60% are also HR+.[20,23] In a 2010 registry of 50,571 patients with breast cancer in the United States, 10.3% of those with a known subtype were HER2+/HR+.[23]

B.1.3.3.1 Breast cancer recurrence in HR+/HER2+ breast cancer

Patients with HR+/HER2+ breast cancer have a persistent risk of disease recurrence, as shown in studies with long-term follow-up.[17,24] The prognosis for women with recurrent HR+/HER2+ breast cancer is poor, as most recurrences involve incurable distant metastatic disease.[17,24]

The use of trastuzumab for patients with early HR+/HER2+ breast cancer in the adjuvant setting has led to a reduction in disease recurrence.[17,24] However, approximately 23% of patients with early HR+/HER2+ breast cancer treated with 1 year of trastuzumab in the HERA trial developed local (4.1%), regional (0.8%), or distant (18%) disease recurrence within 10 years.[17] In a joint analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 studies of HER2+ patients treated with 1 year of trastuzumab and paclitaxel (approximately 55% were also HER2+/HR+), most recurrences were also distant metastatic recurrences (19.2% for the control group and 11.2% for the trastuzumab group).[24]

In the HERA trial, longer treatment with trastuzumab alone (i.e., extending the duration of adjuvant trastuzumab from 1 to 2 years) did not reduce the risk of recurrence compared with 1 year of treatment.[17] The number of HER2+/HR+

patients with any disease event was 236 (27%) after 1 year of trastuzumab and 252 (29%) after 2 years.[17]

Patients with HR+ breast cancer also maintain a persistent rate of recurrence during extended follow-up beyond 10 years, despite being treated with endocrine therapy for 5 years[25,26]:

- A meta-analysis of the results of 88 trials involving 62,923 patients with ER+ breast cancer (HER2+ in 15,418 patients in trials with no use of trastuzumab) who were disease free after 5 years of endocrine therapy from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that there was a persistent risk of recurrence and death from breast cancer for at least 20 years after the original diagnosis. However, PR status (PR+ in 54,115 patients) was not predictive.[25] In patients with known HER2 status, only 2% were scheduled to receive trastuzumab. The patients with HER2+ tumours who did not receive trastuzumab had a worse prognosis in years 0-5 compared with HER2– patients, but not in years 5-20, which may reflect different rates of recurrence in HER2+ patients who do not receive trastuzumab.
- In the International Breast Cancer Study Group (IBCSG) clinical trials, the hazard of recurrence was higher for patients with ER+ disease compared with patients with ER– disease after 5 years (5-10 years: 5.4% vs. 3.3%; 10-15 years: 2.9% vs. 1.3%; 15-20 years: 2.8% vs. 1.2%; and 20-25 years: 1.3% vs. 1.4%; $P < 0.001$; HER2 status unknown).[26]
- In trials assessing efficacy of adjuvant trastuzumab, patients with HER2+/HR+ still relapsed in years 5-10; however, data are not available beyond 10 years.[17]

B.1.3.4 Humanistic burden of breast cancer recurrence

Patients with early breast cancer who experience disease recurrence report significantly poorer health-related quality of life (HRQoL) compared with those who remain disease free,[27,28] while disease progression in patients with metastatic breast cancer has a significantly detrimental impact on HRQoL.[27,29,30] Therapies that reduce the risk of disease recurrence and/or disease progression may help to reduce this impact on patients' HRQoL.

In a matched cohort analysis, women who had a recurrence of breast cancer reported significantly poorer functioning on various HRQoL domains compared with women who had survived breast cancer and remained disease free. Differences were largely due to the poorer HRQoL of women with metastatic disease.[27] Similar results were seen in an observational study that compared women with an initial breast cancer diagnosis or recurrent breast cancer. Compared with patients who

were coping with their first diagnosis, patients with disease recurrence had poorer physical functioning, slower improvements in HRQoL, and higher cancer-related distress. Slower HRQoL recovery was most apparent among younger patients (< 54 years).[28]

A retrospective analysis determined the negative influence of disease progression on HRQoL in patients with metastatic breast cancer. The primary endpoint was minimally important deterioration of global quality of life (QoL) (defined as at least a 5-point decrease in global QoL score). The investigators observed that disease progression had a negative impact on the patient's HRQoL: significantly more patients with progression had a minimally important deterioration compared with patients without progression (adjusted odds ratio for progression status: 2.22; 95% confidence interval [CI], 1.04-4.73; $P = 0.04$).[29] In a similar study, Mayer et al. (2015)[30] measured the impact of metastatic disease on HRQoL in patients beyond the first year of diagnosis. Results indicated that pain, fatigue, and psychological issues continued to be a challenge for patients ≥ 72 months from their metastatic breast cancer diagnosis.

B.1.3.5 Economic burden of breast cancer

The incremental costs of treating breast cancer are significantly higher for advanced-stage disease compared with early-stage disease, but the cost of breast cancer recurrence is also high.[31-36] Treatments that prevent disease recurrence and/or progression may reduce the long-term costs of breast cancer.

In a population-based cost analysis across the European Union, breast cancer had the second highest economic cost of all cancers, equating to €15 billion (12% of the total economic cost of cancer). Total healthcare costs in 2009 for breast cancer for the UK were €581 million, mostly consisting of inpatient care (€233 million) and medication costs (€221 million).[33]

A population-based analysis in England found that women with stage I-II breast cancer have lower costs compared with those with stage III-IV breast cancer. Although lower-stage breast cancer was associated with a higher prevalence of surgery, it was also associated with a shorter in-hospital stay, fewer emergency admissions, and fewer outpatient visits, which result in lower costs.[36]

A UK study in 2007 estimated that aggregate costs of breast cancer recurrence ranged from £10,000 to £40,000 per patient.[35] Karnon et al. (2007)[35] estimated healthcare costs for the treatment of recurrent breast cancer between 1991 and 2004 at Western General Hospital, Edinburgh.[35] Approximately 60% of patients diagnosed with metastases received at least one hormonal therapy, and

approximately half received at least one chemotherapy (almost one-fourth received ≥ 2 chemotherapy regimens). The average number of inpatient days was 24 (interquartile range [IQR], 5-34 days). These high incurred costs are likely to underestimate current NHS costs for treating recurrent breast cancer, as this study was done before the introduction of new approved HER2-directed treatments such as pertuzumab.[37]

B.1.3.6 Treatment pathway

Recommendations for the diagnosis and treatment of early breast cancer in the NHS in England are covered by NICE guideline 101 (NG101).[38]

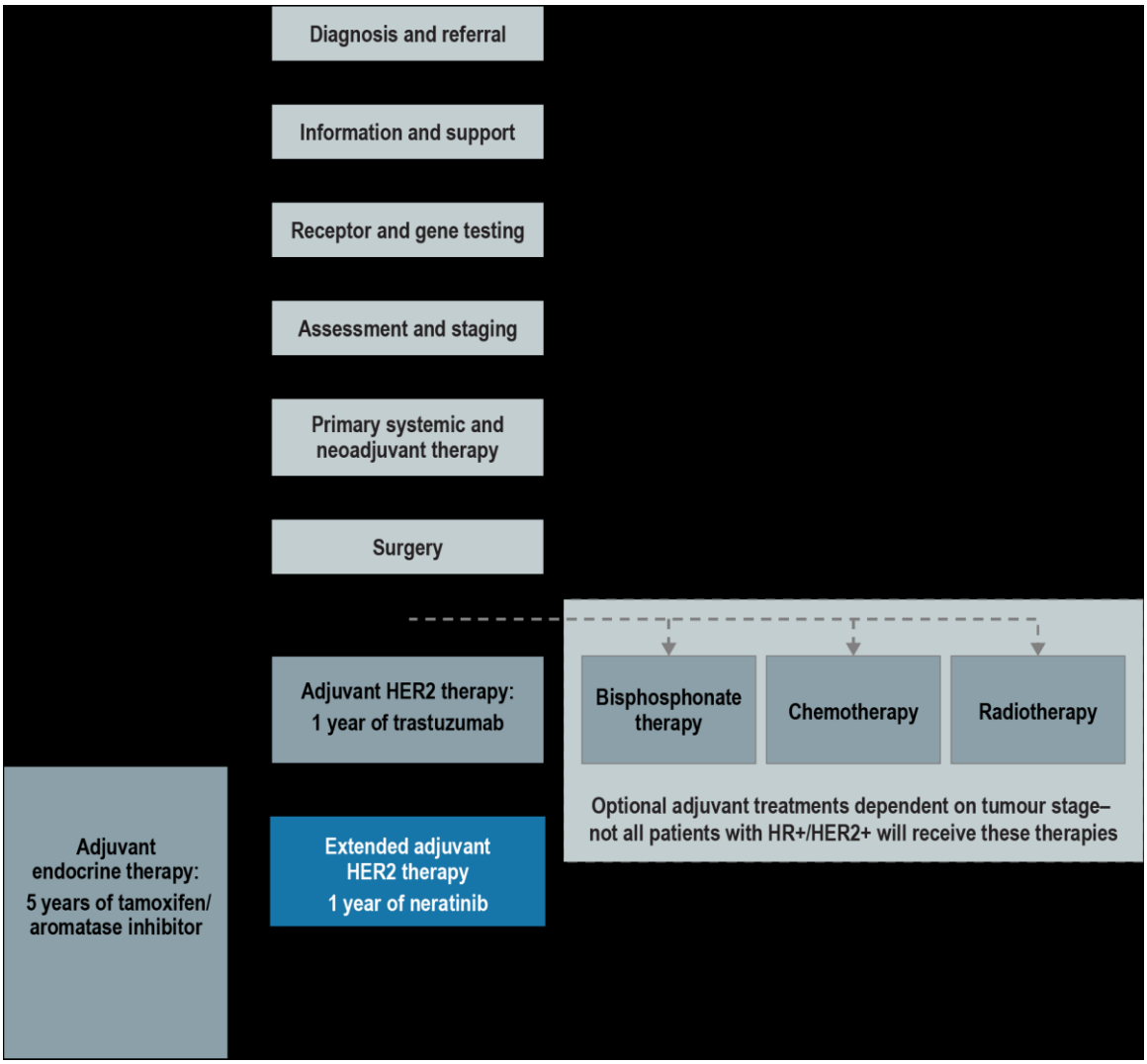
Patients diagnosed with early breast cancer are treated with curative intent. The treatment depends on the type of breast cancer but would generally involve surgery with the addition of drug therapy (including chemotherapy, endocrine therapy, and HER2-directed therapy such as trastuzumab) and radiotherapy, as appropriate. Some patients are subsequently diagnosed with secondary (or metastatic/advanced) breast cancer. The aim of treatment for these patients is to control the cancer, relieve symptoms, and maintain QoL for as long as possible.

According to NICE guideline 101 (NG101), the current standard of care in the NHS for patients with early HER2+ breast cancer after surgery, chemotherapy, and radiotherapy is routine adjuvant therapy with trastuzumab, scheduled as 3-weekly doses for 1 year. Patients with HR+/HER2+ breast cancer also receive adjuvant endocrine therapy, either with tamoxifen or an aromatase inhibitor for 5 years, with the option for extended endocrine therapy beyond 5 years.[38]

Neratinib is positioned as a HER2-directed treatment for patients with early HR+/HER2+ breast cancer in the extended adjuvant setting (i.e., after patients receive 1 year of adjuvant treatment with trastuzumab-based therapy) to reduce the risk of disease recurrence. Using the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS v1.1), neratinib scores an A-rating (best) for adjuvant treatment of early HER2+ breast cancer.[39]

Figure 1 presents the suggested place of neratinib in the NICE pathway for early and locally advanced breast cancer.[40]

Figure 1. Neratinib: place in treatment pathway for early HR+/HER2+ breast cancer



Abbreviations: HER2+, human epidermal growth factor receptor 2-positive; HR+, hormone receptor-positive.

Note: Following surgery, most patients with HR+/HER2+ breast cancer will receive adjuvant trastuzumab and endocrine therapy, with the options of bisphosphonate, chemotherapy, and radiotherapy dependent on tumour stage and clinical judgement.

Adapted from NICE (2018)[40]

Currently, there are no treatment recommendations or approved HER2-directed therapies for people with HR+/HER2+ breast cancer in the extended adjuvant setting after 1 year of treatment with trastuzumab-based therapy, other than endocrine therapy. Adoption of oral neratinib therapy after completion of trastuzumab-based therapy would extend adjuvant HER2-directed therapy for an additional 1 year to reduce the risk of breast cancer recurrence in people with early HR+/HER2+ breast cancer.

B.1.3.7 Unmet clinical need

As 24% of patients with early HR+/HER2+ breast cancer relapse after treatment with adjuvant trastuzumab,[17] there is a need for additional interventions to improve on the benefits of trastuzumab-based therapy, reduce the development of resistance to HER2-targeted agents, and reduce the risk of breast cancer recurrence, disease progression, and death.[6,17,23]

ER signalling appears to be a major compensatory pathway driving the progression of ER+/HER2+ breast cancers treated with HER2 inhibitors.[5] Bidirectional cross talk between ER and HER2 signalling is a potential mechanism of action of endocrine resistance that may be implicated in the development of resistance to HER2-targeted agents and disease recurrence in patients with HR+/HER2+ breast cancer.[5,6] Breast cancer cells may become resistant to trastuzumab because of an extracellular domain–truncated HER2 receptor that can no longer be recognised by the trastuzumab antibody. Other reasons may include alternate survival signalling pathways being activated, such as coactivation of EGFR/HER1 signalling or downstream activation of phosphatidyl-inositol-3-kinase (PI3K) signalling.[41-43]

Alternative HER2-targeting adjuvant regimens used after 1 year of trastuzumab-based therapy have shown limited efficacy in further reducing the risk of recurrence in patients with early HER2+ breast cancer[41-43]:

- In the ALTTO trial, there was no significant improvement in disease-free survival (DFS) when lapatinib was combined with trastuzumab compared with trastuzumab alone (hazard ratio, 0.84; 97.5% CI, 0.70-1.02; *P* = 0.048).[44]
- In the BETH trial, the addition of bevacizumab to trastuzumab-containing regimens did not add any efficacy benefit, and it increased toxicity (hazard ratio, 0.99; 95% CI, 0.79-1.25; *P* = 0.9610).[45]
- In the APHINITY trial, the 3-year rate of invasive disease-free survival (iDFS) was 94.1% with pertuzumab and 93.2% with placebo, equating to a 0.9% absolute benefit with pertuzumab (hazard ratio, 0.81; 95% CI, 0.66-1.00; *P* = 0.045).[46]

After adjuvant trastuzumab, most women in the UK with HER2+ breast cancer do not receive any further therapy, except endocrine therapy for patients with HR+/HER2+ disease.[38] As such, there are no HER2-directed treatments for HR+/HER2+ breast cancer available routinely in the extended adjuvant setting in the UK NHS. Neratinib is an orally administered HER2-targeted therapy and thus obviates the need for administration visits, venous access, and port maintenance without the associated risks of clotting or infection.[1]

B.1.4 Equality considerations

No equality issues or considerations have been identified for neratinib.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was performed in March 2017 according to NICE requirements to identify studies relevant to neratinib for the treatment of early HER2+ breast cancer. The clinical SLR was subsequently updated in November 2018 to identify studies relevant to the updated NICE decision problem: studies of neratinib as extended adjuvant therapy for early HR+/HER2+ breast cancer within 1 year of trastuzumab-based therapy. Once relevant studies were identified, study characteristics, efficacy, HRQoL, and safety data were extracted, and methodologies were critically appraised according to NICE requirements.

See Appendix D for the full search strategy and details of the process and methods used to identify and select the clinical evidence relevant to the submission.

The clinical SLR identified one study for neratinib that was relevant to the NICE decision problem: the Extended Adjuvant Treatment of Breast Cancer With Neratinib (ExteNET) study[47,48] (see Section B.2.2). As the comparator is standard treatment with no further HER2-directed therapy, no other relevant studies were identified.

In addition to ExteNET, the CONTROL study investigated the use of neratinib in people with early HR+/HER2+ breast cancer and is included in the marketing authorisation for neratinib.[1,49-51] This study was not identified in the clinical SLR because it is not a randomised controlled trial (RCT), but it is also relevant to the NICE decision problem and further described in Section B.2.3.2.

B.2.2 List of relevant clinical effectiveness evidence

The clinical effectiveness evidence for neratinib from the two studies identified as relevant to the NICE decision problem and included in the economic model are summarised below and in Table 4. Both studies are ongoing, and future analyses will provide supplementary efficacy and safety evidence for neratinib.

The ExteNET trial (NCT00878709, Study 3144A2-3004-WW) is the pivotal phase 3 RCT that compares extended adjuvant therapy with neratinib versus placebo in people with HER2+ breast cancer, including patients with HR+/HER2+ breast cancer who are within 1 year of completing trastuzumab therapy. ExteNET is currently ongoing: 2-year and 5-year efficacy and safety data have been published in two journal articles.[47,48] A subanalysis of patients relevant to the NICE decision problem (patients with early HR+/HER2+ breast cancer within 1 year of completion of trastuzumab) was presented at the 2018 San Antonio Breast Cancer Symposium

(SABCS).[52] Additional analyses of HRQoL data were presented at ESMO 2017[53] and SABCS 2018[51] and have recently been submitted for publication.[54]

CONTROL (NCT02400476, Study PUMA-NER-6201)[55] is an ongoing phase 2, open-label safety and tolerability study investigating the effect of antidiarrhoeal strategies (such as loperamide prophylaxis) on the incidence and duration of neratinib-associated diarrhoea, the most common side effect observed in the ExteNET trial. Interim analyses were presented at SABCS 2016,[56] SABCS 2017,[50] the 2017 American Association for Cancer Research congress,[49] and SABCS 2018.[51] Data will be submitted for publication when data from all cohorts are mature.

Table 4. Clinical effectiveness evidence for neratinib

Study	ExteNET[47,48,52] (NCT00878709, Study 3144A2-3004-WW)	CONTROL[49-51,55-58] (NCT02400476, Study PUMA-NER-6201)
Study design	Phase 3 multicentre, randomised, double-blind, placebo-controlled trial with 2 groups randomly assigned (1:1), stratified by HR, nodal status, and trastuzumab regimen	Phase 2 open-label safety and tolerability study
Population	Patients with HER2+ breast cancer who have completed 1 year of trastuzumab within 2 years (ITT: N = 2,840). Label population: HR+ completing prior trastuzumab ≤ 1 year from randomisation (n = 1,334).	Patients with HER2+ breast cancer who have completed trastuzumab adjuvant therapy, or experienced side effects resulting in early discontinuation, with last trastuzumab dose given > 2 weeks and < 2 years before enrolment
Intervention(s)	Neratinib (ITT: n = 1,420; label population: n = 670)	Neratinib + loperamide prophylaxis (n = 137) Neratinib + loperamide + budesonide (n = 64) Neratinib + loperamide + colestipol (n = 120) Neratinib + colestipol + loperamide as needed (recruiting) Neratinib dose escalation in cycle 1 + loperamide as needed (recruiting) Neratinib dose escalation in cycle 2 + loperamide as needed (recruiting)
Comparator(s)	Placebo (ITT: n = 1,420; label population: n = 664)	Neratinib + no mandatory loperamide (ExteNET historical comparator: n = 1,420)
Trial supports MA?	Yes	Yes
Trial used in the economic model?	Yes	Yes
Rationale for use/ non-use in model	This is the pivotal trial for neratinib using the licensed dose and indicated patient population. Efficacy and safety results were used in the model.	This is a phase 2 safety study investigating the tolerability of neratinib with antidiarrhoeal prophylaxis. Rates of AEs were used in the model.
Reported outcomes specified in the decision problem (bold indicated included in model)	Primary endpoint: **iDFS** Secondary endpoints: DFS-DCIS, TTDR, distant DFS, OS, incidence of CNS recurrence and **AEs (including incidence of grade ≥ 3 diarrhoea)** Exploratory endpoints: PROs (FACT-B and **EQ-5D-3L**)	Primary endpoint: incidence of grade ≥ 3 diarrhoea during treatment with neratinib Secondary endpoints: frequency distribution of maximum-grade diarrhoea; **duration, incidence, and severity of diarrhoea by loperamide exposure**, with and without anti-inflammatory agents, with and without a bile acid sequestrant; serious AEs; AEs of interest Exploratory endpoints: PROs (FACT-B and EQ-5D-5L)

Abbreviations: AE, adverse event; CNS, central nervous system; DCIS, ductal carcinoma in situ; FACT-B, Functional Assessment of Cancer Therapy–Breast; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; ITT, intention-to-treat population (all randomised patients); MA, marketing authorisation; OS, overall survival; PRO, patient-reported outcome; TTDR, time to distant recurrence.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 ExteNET

B.2.3.1.1 ExteNET methodology

ExteNET is the pivotal phase 3 RCT providing the key efficacy and safety data for neratinib included in the economic model. Table 5 presents details of the ExteNET methodology; further details on endpoints and statistical analysis are described in Section B.2.4.

Table 5. ExteNET: summary of trial methodology

Location	495 sites in 40 countries in Europe, Asia, Australia, New Zealand, North America, and South America (13 sites in the UK)	
Trial design	International, multicentre, randomised, double-blind, placebo-controlled phase 3 trial	
Eligibility criteria for participants	Inclusion criteria: ▪ Female patients aged ≥ 18 years (for Japan aged ≥ 20 years) with ECOG performance status of 0 to 1. ▪ Corrected QT interval ≤ 0.450 seconds and LVEF within institutional range of normal; performed by multigated acquisition or echocardiogram. ▪ Histologically confirmed primary adenocarcinoma of the breast that was HER2+ by 1 of 3 protocol-defined assays (performed locally). ▪ Primary tumour ER/PR status was known before study entry. ▪ Diagnosis of stage II-IIIC primary breast cancer with axillary node-positive disease.[59] Note that patients who completed neoadjuvant therapy and had residual invasive disease only in the breast, with negative or unknown nodal status, were eligible. ▪ Clinical and radiologic assessments that were negative for local or regional recurrence of disease or metastatic disease at the time of study entry. ▪ Adequately treated primary breast cancer with surgery, as defined by prior mastectomy or lumpectomy, with margins clear of invasive carcinoma and DCIS. Patients with	Exclusion criteria: ▪ Pregnant or breastfeeding women. ▪ Unstable angina, congestive heart failure (NYHA class II, III, or IV, including patients who currently use digitalis, beta blockers, or calcium channel blockers specifically for congestive heart failure), ventricular arrhythmia requiring medical therapy, a history of myocardial infarction within 12 months, QTc interval > 0.450 seconds or known history of QTc prolongation or torsades de pointes, or a history of idiopathic ventricular tachycardia or ventricular fibrillation. ▪ Active unresolved infections. ▪ Significant chronic gastrointestinal disorder with diarrhoea as a major symptom (e.g., Crohn disease, ulcerative colitis, malabsorption, or grade ≥ 2 diarrhoea of any aetiology at baseline). ▪ Clinical or radiologic evidence of local or regional recurrence of disease or metastatic disease before or at the time of study entry. ▪ pCR in breast and axilla (if axillary status is known) or if they have only residual in situ disease in breast (DCIS) and pCR in axilla (if axillary status is known). ▪ Metachronous invasive or metachronous DCIS breast cancer (i.e., primary breast cancers

	positive sentinel node biopsies who had subsequent axillary dissection. ▪ Completion of a course of prior adjuvant trastuzumab: – If < 12 months of trastuzumab had been given, at least 8 prior doses of weekly trastuzumab or at least 3 prior doses of trastuzumab given every 3 weeks was administered. – The last dose of trastuzumab was given > 2 weeks and ≤ 1 year from randomisation (Amendment 3 criteria). ▪ If patients had prior neoadjuvant therapy (chemotherapy with or without neoadjuvant trastuzumab, regardless of nodal status at initial diagnosis), they were eligible provided they had residual invasive cancer in the breast and/or axilla after completing neoadjuvant therapy. ▪ Completion of neoadjuvant or adjuvant chemotherapy regimen containing an anthracycline and/or a taxane or any cyclophosphamide, methotrexate, and 5-fluorouracil regimen. ▪ Ineligible or unable to receive further adjuvant trastuzumab based on either of the following: – Completion of intended treatment course of adjuvant trastuzumab based on published data (FinHer regimen). – Side effects that resulted in early discontinuation of trastuzumab that have since resolved.	diagnosed at different times > 6 months apart). ▪ Second malignancy, other than adequately treated non–melanoma skin cancers, in situ melanoma, or in situ cervical cancer. Patients with other non-mammary malignancies had to be disease free for ≥ 5 years. ▪ Prior therapy with an HER1 and/or HER2 inhibitor other than trastuzumab. ▪ Any prior mediastinal irradiation except internal mammary node irradiation for the present breast cancer. ▪ Currently receiving chemotherapy, radiation therapy, immunotherapy, or biotherapy for breast cancer. ▪ On treatment or in follow-up of any other neoadjuvant or adjuvant breast cancer trial with DFS as an endpoint.
Settings and locations where the data were collected	See location	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n = [x]) and comparator(s) (n = [x])**	Placebo (ITT: n = 1,420) or neratinib 240 mg (ITT: n = 1,420) taken orally, once daily continuously for 12 months. Treatment was given for 12 months unless disease recurrence or new breast cancer, intolerable adverse events, or consent withdrawal occurred. Neratinib dose reductions (200 mg, 160 mg, and 120 mg per day) were allowed for toxicity, with treatment cessation if the lowest dose was not tolerated or if treatment was interrupted for > 3 weeks. Dose reductions were mandated for grade 3 diarrhoea after resolution to grade 1 or lower within 3 weeks, if a second episode of grade 3 diarrhoea occurred despite optimum medical therapy, and in the event of symptomatic grade 2 pneumonitis or interstitial lung disease and other grade 3 non-haematological events after resolution to grade 1 or lower within 3 weeks.	

Permitted and disallowed concomitant medication	Concurrent adjuvant endocrine therapy for HR+ disease was recommended. The following treatments were prohibited throughout the duration of the treatment phase of the study: ▪ Any chemotherapy, radiation therapy, immunotherapy, biotherapy, or surgery for breast cancer ▪ Any other investigational agent The following treatments were permitted during the study: ▪ Standard therapies for preexisting medical conditions and for medical and/or surgical complications. ▪ Adjuvant endocrine therapy for HR+ disease. ▪ Bisphosphonates, regardless of the indication. ▪ Raloxifene or other selective ER modulators are not prohibited for use in approved indications (i.e., prevention or treatment of osteoporosis or osteopenia in postmenopausal women). Raloxifene is not approved for the adjuvant treatment of breast cancer and is not to be used for this purpose during a subject's participation in this trial. Other: ▪ Subjects should avoid drugs known to be strong cytochrome P450 3A4 inducers or inhibitors (e.g., ketoconazole) for the duration of the treatment phase of the study. Subjects should also avoid grapefruit juice and herbal remedies, including St. John's wort. ▪ Subjects on coumarin-derivative anticoagulants (e.g., warfarin) should be monitored closely and their anticoagulant dose adjusted as needed. ▪ Subjects must be instructed to treat diarrhoea at its earliest occurrence. If significant diarrhoea persists, prophylactic loperamide or other antidiarrhoeal medications are recommended. ▪ Subjects on chronic laxatives should be followed closely and consideration should be given to decreasing or stopping laxatives prior to starting investigational agent, given the potential for neratinib-related diarrhoea to be worsened by concomitant laxative use. ▪ Drugs known to cause QTc prolongation that are being given concomitantly require close monitoring of the subject with serial electrocardiograms. ▪ Subjects on digoxin, a P-glycoprotein substrate with a narrow therapeutic window, should be monitored closely and their digoxin dose adjusted as needed because neratinib is an inhibitor of P-glycoprotein. Coadministration of neratinib and digoxin could result in increased digoxin levels and associated digoxin toxicity. ▪ Elective surgery, such as breast reconstruction, should be avoided while receiving investigational product. If surgery is required, the recommendation is to hold investigational product for 3-4 days before surgery and then resume product when the subject is tolerating a full diet postoperatively (no later than 3 weeks after holding it).
Primary outcomes (including scoring methods and timings of assessments)	Primary endpoint: iDFS at 2 years after randomisation, in which invasive disease was defined as time from randomisation to the first occurrence of the following events: ▪ Invasive ipsilateral breast tumour recurrence ▪ Invasive contralateral breast cancer ▪ Local/regional invasive recurrence ▪ Distant recurrence ▪ Death from any cause Any patient for whom an event had not been observed by the data cutoff was censored at the date of their last physical examination.
Other outcomes used in the economic	Secondary endpoints were DFS-DCIS, time to distant recurrence, DDFS, cumulative incidence of CNS recurrences, overall survival, and safety. All time-to-event secondary endpoints were defined as from time of randomisation.

model/specified in the scope	Health-related quality of life was an exploratory endpoint, with the EQ-5D-3L and FACT-B version 4, at baseline and months 1, 3, 6, 9, and 12 (end of treatment).
Preplanned subgroups	The primary efficacy analysis was conducted on the ITT population, consisting of all subjects randomised. Prespecified subgroup analyses also included the following: ▪ HR status (HR+ [defined as ER+ or PR+, or both] vs. HR– [defined as ER– and PR–]) ▪ Nodal status (0 vs. 1-3 vs. 4 or more) ▪ Trastuzumab adjuvant regimen (sequentially vs. concurrently with chemotherapy) ▪ All subjects who completed prior trastuzumab ≤ 1 year vs. > 1 year from randomisation ▪ Amended ITT of higher risk patients: (defined as all patients with node-positive disease who were randomly assigned within 1 year of completing previous trastuzumab) ▪ All subjects with node-positive disease ▪ All subjects who were HER2+ based on central testing

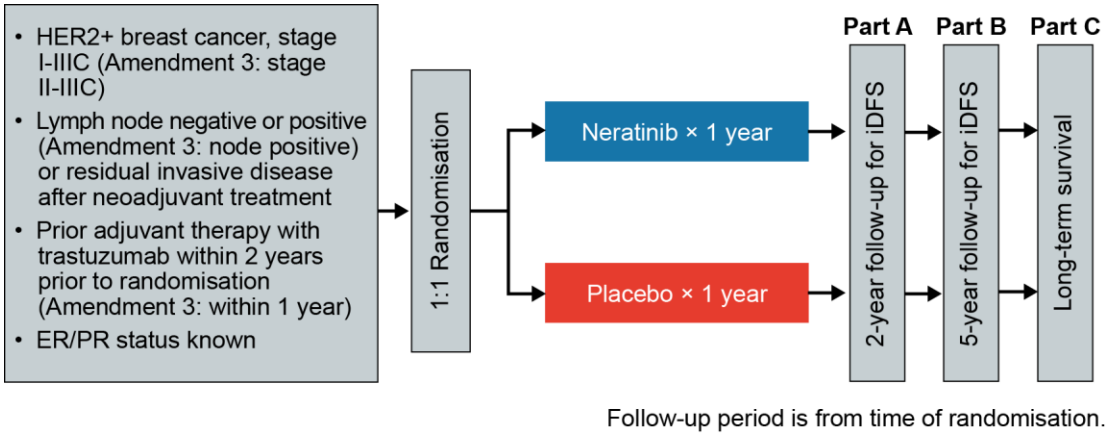
Abbreviations: CNS, central nervous system; DCIS, ductal carcinoma in situ; DDFS, distant disease-free survival; DFS, disease-free survival; DFS-DCIS, disease-free survival including ductal carcinoma in situ; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; FACT-B, Functional Assessment of Cancer Therapy–Breast; FinHer, Finland Herceptin trial; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; ITT, intention to treat; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; pCR, pathological complete response; PR, progesterone receptor.

Sources: Chan et al. (2016)[48]; Puma data on file (2014)[60]

B.2.3.1.2 ExteNET: trial design and protocol amendments

ExteNET is an ongoing, phase 3 RCT comparing extended adjuvant therapy with neratinib versus placebo in women with early-stage HER2+ breast cancer who have previously received adjuvant trastuzumab. Participants were randomised in a 1:1 ratio to receive either neratinib or placebo daily for 1 year (Figure 2). Protocol amendments are further described in Table 6.

Figure 2. ExteNET trial design



Abbreviations: ER, oestrogen receptor; HER2+, human epidermal growth factor receptor 2-positive; iDFS, invasive disease-free survival; PR, progesterone receptor.

Note: As of Amendment 9, after discontinuing study treatment, patients were followed for disease recurrence and survival for 2 years after randomisation. With Amendment 13, recurrent disease events and deaths were determined for the intention-to-treat population as follows:

Part A: Full physical examinations at baseline and 1 year and physical examinations, including breast and axillary examinations every 3 months while on treatment and every 4 months during follow-up until the end of year 2.
Part B: Expansion of follow-up from 2 to 5 years (+ 90 days) postrandomisation. Recurrent disease events and deaths were determined from patients' medical records upon reconsent of the patients. Statistical evaluations for this part of the study are considered to be sensitivity analyses.
Part C: Long-term follow-up of overall survival until 248 deaths have occurred.

Sources: Puma data on file (2016)[61]; Chan et al. (2016)[48]; Martin et al. (2017)[47]

Randomisation was stratified by the following three factors[47,48,61]:

- HR+ (ER+ and/or PR+) versus HR– (ER– and PR–)
- Nodal status (0, 1-3 vs. 4 or more positive nodes):
  - Patients with residual invasive disease in the breast but node-negative or unknown nodal status in the axilla after neoadjuvant therapy were included under "1-3" positive nodes.
  - In Amendment 3, the inclusion criteria for breast cancer staging and nodal status were revised to include only patients with stage II-IIIC and only patients with axillary node-positive disease.
- Prior trastuzumab given sequentially versus concurrently with chemotherapy:
  - Trastuzumab given sequentially was defined as any regimen in which trastuzumab was started after completion of cytotoxic chemotherapy (e.g., doxorubicin + cyclophosphamide followed by paclitaxel followed by trastuzumab monotherapy for 1 year).
  - Trastuzumab given concurrently with chemotherapy was defined as any regimen in which trastuzumab was started while chemotherapy was being given (e.g., doxorubicin + cyclophosphamide followed by trastuzumab + paclitaxel followed by trastuzumab monotherapy to complete 1 year of trastuzumab).

During the course of the ExteNET study, the original protocol (29 April 2009) had a total of six global protocol amendments under the supervision of three sponsors, with the last amendment (Amendment 13) occurring in January 2014.[48] Three of the global protocol amendments affected the original trial design and are described below and in Table 6.

Table 6. ExteNET protocol amendments affecting trial design

	Original Protocol 29 Apr 2009 (Wyeth)	Amendment 3 25 Feb 2010 (Pfizer)	Amendment 9 14 Oct 2011 (Pfizer)	Amendment 13 Oct 2013 (Puma)
Planned sample size	3,850	3,300	2,840 (recruitment was stopped)	2,840

	Original Protocol 29 Apr 2009 (Wyeth)	Amendment 3 25 Feb 2010 (Pfizer)	Amendment 9 14 Oct 2011 (Pfizer)	Amendment 13 Oct 2013 (Puma)
Patient population for the primary analysis	▪ ITT ▪ < 2 years from trastuzumab ▪ Node positive or negative	▪ **Amended ITT** ▪ < 1 year from trastuzumab ▪ Node positive	▪ Amended ITT ▪ < 1 year from trastuzumab ▪ Node positive	▪ **ITT restored to per protocol primary objective** ▪ < 2 years from trastuzumab ▪ Node positive or negative
Primary endpoint	iDFS	iDFS	iDFS	iDFS
Planned analyses	▪ iDFS events: – First interim analysis: 135 – Second interim analysis: 236 – Final: 337 ▪ 90% power to detect a difference in iDFS if the hazard ratio was 0.70 in favour of neratinib	▪ No prespecified target iDFS events ▪ 90% power to detect a difference in iDFS if the hazard ratio was 0.713 in favour of neratinib	▪ No prespecified target iDFS events ▪ 83% power to detect a difference in iDFS if the hazard ratio was 0.667 in favour of neratinib	▪ No prespecified target iDFS events ▪ 88% power to detect a difference in iDFS if the hazard ratio was 0.667 in favour of neratinib
Follow-up time (years)	5	5	2	▪ Primary: 2 ▪ Descriptive: 5
Secondary endpoint (OS analysis)	Analysis at the 5-year follow-up	Analysis at DFS and 5-year follow-up	**Analysis at the 2-year follow-up**	▪ Primary analysis at 248 events ▪ Interim analysis at 124 events

Abbreviations: DFS, disease-free survival; iDFS, invasive disease-free survival; ITT, intention to treat; OS, overall survival.

Sources: Chan et al. (2016)[48]; Martin et al. (2017)[47]; Puma data on file (2016)[61]

Global Protocol Amendment 3

After study commencement, long-term follow-up data were presented for two adjuvant trastuzumab trials, NCCTG N9831 and Breast Cancer International Research Group (BCIRG) 006.[62,63] In both trials, the 5-year DFS rate was reported to be approximately 84% for patients treated with adjuvant chemotherapy followed by a taxane plus trastuzumab, which confirmed a risk of tumour recurrence for patients who completed adjuvant trastuzumab therapy. However, the 5-year DFS rate for node-negative cancer treated with adjuvant chemotherapy followed by a taxane plus trastuzumab reported in the BCIRG 006 study was 93%, indicating the recurrence risk was lower than when ExteNET was designed. Additional efficacy data from more mature pivotal adjuvant trastuzumab trials also suggested that patients were at higher risk of recurrence closer to completion of adjuvant trastuzumab and that the

risk of recurrence may decrease over time. As a result, ExteNET was amended to include only patients with a higher risk of recurrence (node positive and stage II-IIIC), and patients were to be randomised within 1 year of completion of trastuzumab therapy (i.e., the amended intention-to-treat [ITT] population).[48]

Global Protocol Amendment 9

The trial sponsor at that time chose to stop enrolment of new patients, and follow-up was limited to 2 years after randomisation, which affected the original study objectives of evaluating the long-term efficacy of neratinib in the extended adjuvant setting.[48]

Global Protocol Amendment 13

Amendment 13 was made after the publication of results of the I-SPY-2 study, which compared neratinib with standard neoadjuvant therapy for high-risk stage II/III breast cancer.[64] I-SPY-2 showed the pathological complete response rate for paclitaxel plus neratinib was higher than for paclitaxel plus trastuzumab. Amendment 13 restored ExteNET to its primary objective—that is, to obtain iDFS and overall survival (OS) data for all randomised patients to evaluate the long-term efficacy of neratinib in the extended adjuvant setting. Collection of recurrent disease events was re-established to 5 years after randomisation, and the primary efficacy analysis was returned to the ITT population.[48]

B.2.3.1.3 ExteNET: baseline characteristics

The ITT population of ExteNET included patients with HER2+ breast cancer regardless of HR status or time from completion of trastuzumab therapy; however, the authorised marketing indication for neratinib (the label population) is narrower: patients with HR+/HER2+ breast cancer who have completed a course of adjuvant trastuzumab less than 1 year ago.

Table 7 and Table 8 present baseline characteristics of the ITT population and the label population, respectively. Baseline characteristics were similar between both populations, with no notable differences of distribution between treatment arms. Overall, 46.97% (1,334/2,840) of the ITT population in ExteNET met the criteria of the label population: HR+/HER2+ breast cancer and also completing a course of trastuzumab within 1 year.

In ExteNET, the median age in the ITT population was 52.3 years (≥ 50 years, 59.9%; ≥ 65 years, 12.3%); 81.0% were white, 2.6% black or African American, 13.6% Asian, and 2.9% other. At baseline, 57.4% had HR+ disease (defined as ER+ and/or PR+), 23.6% were node negative, 46.8% had one to three positive nodes,

and 29.6% had four or more positive nodes. Approximately 10% of patients had stage I tumours, approximately 40% had stage II tumours, and approximately 30% had stage III tumours. Median time from the last adjuvant trastuzumab treatment to randomisation was 4.5 months.[1] For HR+ patients, the majority of patients had been treated previously with endocrine therapy and concurrent adjuvant endocrine therapy was recommended during the trial period. Concomitant endocrine therapy during ExteNET was similar between treatment arms in both the ITT and label populations.[65,66]

Patient disposition and flow in the ExteNET trial are described in more detail in Appendix D.

Table 7. ExteNET: baseline patient characteristics, intention-to-treat population

Characteristic	Neratinib (n = 1,420) n (%)	Placebo (n = 1,420) n (%)
Region		
North America	519 (37%)	477 (34%)
Western Europe, Australia, and South Africa	487 (34%)	532 (38%)
Asia Pacific, Eastern Europe, and South America	414 (29%)	411 (29%)
Age, years (median [range])	52 (25-83)	52 (23-82)
Menopausal status at diagnosis		
Premenopausal	663 (47%)	664 (47%)
Postmenopausal	757 (53%)	756 (53%)
Nodal status[a]		
Negative	335 (24%)	336 (24%)
1-3 positive nodes	664 (47%)	664 (47%)
≥ 4 positive nodes	421 (30%)	420 (30%)
HR status		
Positive (ER+, PR+, or both)	816 (58%)	815 (57%)
Negative (ER– and PR–)	604 (43%)	605 (43%)
Previous trastuzumab regimen		
Given concurrently with chemotherapy	884 (62%)	886 (62%)
Given sequentially with chemotherapy	536 (38%)	534 (38%)
T stage		
T1	440 (31%)	459 (32%)
T2	585 (41%)	555 (39%)
≥ T3	144 (10%)	117 (8%)
Unknown	250 (18%)	288 (20%)
Missing	1 (< 1%)	1 (< 1%)
Prior neoadjuvant or adjuvant therapy[b]		
Trastuzumab	1,420 (100%)	1,420 (100%)

Characteristic	Neratinib (n = 1,420) n (%)	Placebo (n = 1,420) n (%)
Anthracycline only	136 (10%)	135 (10%)
Anthracycline plus taxane	962 (68%)	965 (68%)
Taxane only	318 (22%)	316 (22%)
Neither anthracycline or taxane	4 (< 1%)	4 (< 1%)
Duration of prior adjuvant trastuzumab therapy, months (median [range])	11.5 (10.9-11.9)	11.4 (10.8-11.9)
Time from last dose of trastuzumab to randomisation, months (median [IQR])	4.4 (1.6-10.4)	4.6 (1.5-10.8)
Prior endocrine therapy use for HR+ tumours,[c] n (%)		
No	56 (7%)	51 (6%)
Yes	760 (93%)	764 (94%)
Antioestrogen only	375 (46%)	347 (43%)
Antioestrogen and aromatase inhibitor (sequential)	20 (3%)	34 (4%)
Aromatase inhibitor only	362 (44%)	379 (47%)
Non–antioestrogen or aromatase inhibitor	3 (< 1%)	4 (< 1%)

Abbreviations: ER, oestrogen receptor; HR, hormone receptor; IQR, interquartile range; PR, progesterone receptor.

[a] The number of positive nodes was at the time of initial diagnosis (for patients who received adjuvant therapy) or surgery (for those who received neoadjuvant therapy). Patients with residual invasive disease in the breast, but node-negative disease or unknown nodal status in the axilla, after neoadjuvant therapy were included under 1-3 positive nodes.

[b] The proportion of patients who received neoadjuvant chemotherapy was 25% (n = 247) in the neratinib group and 27% (n = 282) in the placebo group.

[c] Percentage is based on the number of patients with HR+ tumours. Tumours were assessed as being ER+ or PR+ on the basis of local pathology laboratory cutoffs. There was no protocol specification as to whether a 1% or 10% threshold should be used.

Adapted from Martin et al. (2017)[47]

Table 8. ExteNET: baseline patient characteristics, label population (HR+ completing prior trastuzumab ≤ 1 year from randomisation)

Characteristic	Neratinib (n = 670) n (%)	Placebo (n = 664) n (%)
Region		
North America	237 (35.4)	205 (30.9)
Western Europe, Australia, and South Africa	236 (35.2)	264 (39.8)
Asia Pacific, Eastern Europe, and South America	197 (29.4)	195 (29.4)
Age, years (median [range])	51 (25-83)	51 (23-78)
Menopausal status at diagnosis		
Premenopausal	350 (52.2)	342 (51.5)
Postmenopausal	320 (47.8)	322 (48.5)
Nodal status[a]		

Characteristic	Neratinib (n = 670) n (%)	Placebo (n = 664) n (%)
Negative	130 (19.4)	125 (18.8)
1-3 positive nodes	339 (50.6)	334 (50.3)
≥ 4 positive nodes	201 (30.0)	205 (30.9)
Previous trastuzumab regimen		
Concurrent with chemotherapy	411 (61.3)	415 (62.5)
Sequential with chemotherapy	259 (38.7)	249 (37.5)
T stage		
T1	218 (32.5)	209 (31.5)
T2	270 (40.3)	250 (37.7)
≥ T3	61 (9.1)	65 (9.8)
Unknown	121 (18.1)	140 (21.1)
Prior neoadjuvant or adjuvant therapy[b]		
Trastuzumab	670 (100.0)	664 (100.0)
Anthracycline only	67 (10.0)	58 (8.7)
Anthracycline plus taxane	435 (64.9)	445 (67.0)
Taxane only	167 (24.9)	159 (23.9)
Neither anthracycline or taxane	1 (0.1)	2 (0.3)
Duration of prior adjuvant trastuzumab therapy, months (median [range])	11.4 (1.4-29.1)	11.4 (1.4-24.0)
Time from last dose of trastuzumab to randomisation, months (median [range])	3.07 (0.2-12.0)	3.30 (0.3-12.0)
Prior endocrine therapy use for HR+ tumours,[c] n (%)		
No	38 (5.7)	30 (4.5)
Yes	632 (94.3)	634 (95.5)
Antioestrogen only	340 (50.7)	317 (47.7)
Antioestrogen and aromatase inhibitor (sequential)	29 (4.3)	24 (3.6)
Aromatase inhibitor only	259 (38.7)	290 (43.7)
Non–antioestrogen or aromatase inhibitor	4 (0.6)	3 (0.5)

Abbreviations: HR, hormone receptor.

[a] The number of positive nodes was at the time of initial diagnosis (for patients who received adjuvant therapy) or surgery (for those who received neoadjuvant therapy). Patients with residual invasive disease in the breast, but node-negative disease or unknown nodal status in the axilla, after neoadjuvant therapy were included under 1-3 positive nodes.

[b] The proportion of patients who received neoadjuvant chemotherapy was 24.2% (n = 162) in the neratinib group and 28.9% (n = 192) in the placebo group.

[c] From stratification factors.

Source: Gnant et al. (2018)[52]

B.2.3.2 CONTROL

B.2.3.2.1 CONTROL: methodology

CONTROL is an ongoing, phase 2, open-label safety and tolerability study investigating the effect of structured antidiarrhoeal strategies (such as loperamide prophylaxis with or without budesonide or colestipol) on the incidence of neratinib-associated diarrhoea, the most common side effect observed in the ExteNET trial.[55] Safety data for neratinib from CONTROL are included in the economic model to reflect the incidence of diarrhoea with neratinib when initiated with an antidiarrhoeal medication, as instructed in the label.[1] Table 9 presents details of the CONTROL methodology; further details on endpoints and statistical analysis are described in Section B.2.4.

Table 9. CONTROL: summary of trial methodology

Location	52 sites in the US, Canada, Australia, and Spain	
Trial design	Open-label, phase 2 safety and tolerability study comparing neratinib + antidiarrhoeal prophylaxis (such as loperamide with or without budesonide or colestipol) vs. a historical cohort of neratinib without protocol-mandated antidiarrhoeal prophylaxis	
Eligibility criteria for participants	Inclusion criteria: ▪ Aged ≥ 18 years ▪ Histologically confirmed stage I-IIIC primary adenocarcinoma of the breast ▪ Documented HER2 overexpression or gene-amplified tumour by a validated method ▪ Completed a prior course of adjuvant trastuzumab or experienced side effects that resulted in early discontinuation of trastuzumab that have since resolved ▪ The last dose of trastuzumab must have been given > 2 weeks and < 2 years (365 days) from enrolment ▪ Clinical and radiologic assessments that were negative for local or regional recurrence of disease or metastatic disease at the time of study entry ▪ LVEF ≥ 50% measured by multiple-gated acquisition scan or echocardiogram ▪ ECOG status of 0 to 1 ▪ Recovery (i.e., to grade 1 or baseline) from all clinically	Exclusion criteria: ▪ Clinical or radiologic evidence of local or regional recurrence of disease or metastatic disease prior to or at the time of study entry ▪ Currently receiving chemotherapy, radiation therapy, immunotherapy, or biotherapy for breast cancer ▪ Major surgery < 30 days before starting treatment, or received chemotherapy, investigational agents, or other cancer therapy < 14 days before the initiation of investigational products ▪ Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure, unstable angina, myocardial infarction within 12 months of enrolment, or ventricular arrhythmia ▪ QTc interval > 0.450 seconds (females) or known history of QTc prolongation or torsade de pointes ▪ Screening laboratory assessments outside protocol-defined limits ▪ Active unresolved infections ▪ Patients with a second malignancy, other than adequately treated non–melanoma skin cancers, in situ melanoma, or in situ cervical cancer. Patients with other non-

	significant AEs related to prior therapies (excluding alopecia, neuropathy, and nail changes).	mammary malignancies must have been disease free for ≥ 15 years ▪ Significant chronic gastrointestinal disorder with diarrhoea as a major symptom ▪ Clinically active infection with hepatitis B or hepatitis C virus
Settings and locations where the data were collected	See location	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n = [x]) and comparator(s) (n = [x])** **Permitted and disallowed concomitant medication**	1. Neratinib + loperamide (n = 137, loperamide cohort) 2. Neratinib + loperamide + budesonide (n = 64, budesonide cohort) 3. Neratinib + loperamide + colestipol (n = 120, colestipol cohort) 4. Neratinib + colestipol + loperamide as needed (recruitment ongoing) 5. Neratinib dose escalation during cycle 1 + loperamide as needed (recruitment ongoing) 6. Neratinib dose escalation during cycle 2 + loperamide given as needed (recruitment ongoing) 7. Neratinib-only historical cohort from ExteNET (n = 1,420, ExteNET cohort, no protocol-mandated loperamide) Loperamide cohort: oral neratinib 240 mg/day for 1 year—thirteen 28-day cycles (with or without hormone therapy as indicated), with oral loperamide prophylaxis (4 mg, 2 tablets/capsules taken 3 times daily) for the first two 28-day cycles and then loperamide (≤ 16 mg/day) as needed after completion of loperamide prophylaxis. Budesonide cohort: oral neratinib 240 mg/day for 1 year—thirteen 28-day cycles (with or without hormone therapy as indicated), with oral budesonide (9 mg daily in the morning) for the first 28-day cycle plus loperamide prophylaxis for the first two 28-day cycles and then as needed, as described above. Colestipol cohort: oral neratinib 240 mg/day for 1 year—thirteen 28-day cycles (with or without hormone therapy as indicated), plus oral colestipol (two 1 g tablets taken twice daily) for 1 cycle plus loperamide prophylaxis as described above for 1 cycle and thereafter as needed. Cohort 4: 240 mg neratinib orally once daily with food for thirteen 28-day cycles. Colestipol for 1 cycle and loperamide to be administered as needed. Cohort 5: 120 mg neratinib for week 1, followed by 160 mg neratinib starting at week 2, followed by 240 mg neratinib starting at week 3 and thereafter (C1D15 to end of treatment). Loperamide administered as needed. Cohort 6: 160 mg neratinib for the first 2 weeks, followed by 200 mg neratinib for the next 2 weeks, followed by 240 mg neratinib thereafter (C2D1 to end of treatment). Loperamide will be administered on an as-needed basis only. Treatment-emergent diarrhoea managed with pharmacological treatments (i.e., loperamide or diphenoxylate plus atropine), dietetic measures (discontinuing lactose-containing products; drinking 8-10 large glasses of clear liquids/day; eating frequent small meals; low-fat regimen enriched with bananas, rice, apple sauce, and toast), and neratinib dose modifications (dose holds or reductions, according to a protocol-defined schedule). If doses of neratinib were held, study procedures for that cycle proceeded on schedule as planned, without any delay. Missed dose(s) of neratinib (i.e., any dose[s] not administered within the protocol-defined administration window) was not made up. The dose-adjustment guidelines represent the minimum set of measures investigators were required to follow; additional measures could be taken, as necessary, for certain	

	patients per the investigator's medical judgement. All dose modifications/ adjustments were documented. Once the neratinib dose was reduced for a patient, all subsequent cycles were administered at that dose, unless further dose reduction was required. Dose re-escalation was only permitted if explicitly approved in advance by the study sponsor. Evidence of such approval had to be contained within the patient's source file. Patients with symptomatic constipation were instructed to hold the loperamide dose until after the first bowel movement and resume prophylaxis with reduced-dose loperamide; budesonide was continued if loperamide doses were held because of constipation.
Primary outcomes (including scoring methods and timings of assessments)	Primary endpoint: incidence of grade ≥ 3 diarrhoea during treatment with neratinib. All safety analyses were descriptive. Patients were seen on day 1 of cycles 1, 2, 3, 4, 7, and 10 and at the end of cycle 13 and contacted by telephone on days 1-3 after the first neratinib dose to inquire about diarrhoea or other potential AEs, receive guidance on AE management, and confirm the first date of neratinib dosing. Patients used a diary to record study medication intake. Follow-up continued for 28 days after the last neratinib dose.
Other outcomes used in the economic model/specified in the scope	Secondary endpoints included: ▪ Evaluation of the association between antidiarrhoeal treatment exposure and incidence and severity of diarrhoea (such as loperamide with or without budesonide or colestipol) ▪ Assessment of the incidence of serious AEs and other AEs of special interest Exploratory endpoint: HRQoL, including the EQ-5D-5L and FACT-B version 4 questionnaires completed electronically on day 1 of cycles 1, 2, 4, 7, and 10 and at the end of cycle 13 (end of treatment). HRQoL assessments were introduced in November 2015 (protocol Amendment 2).
Preplanned subgroups	None specified

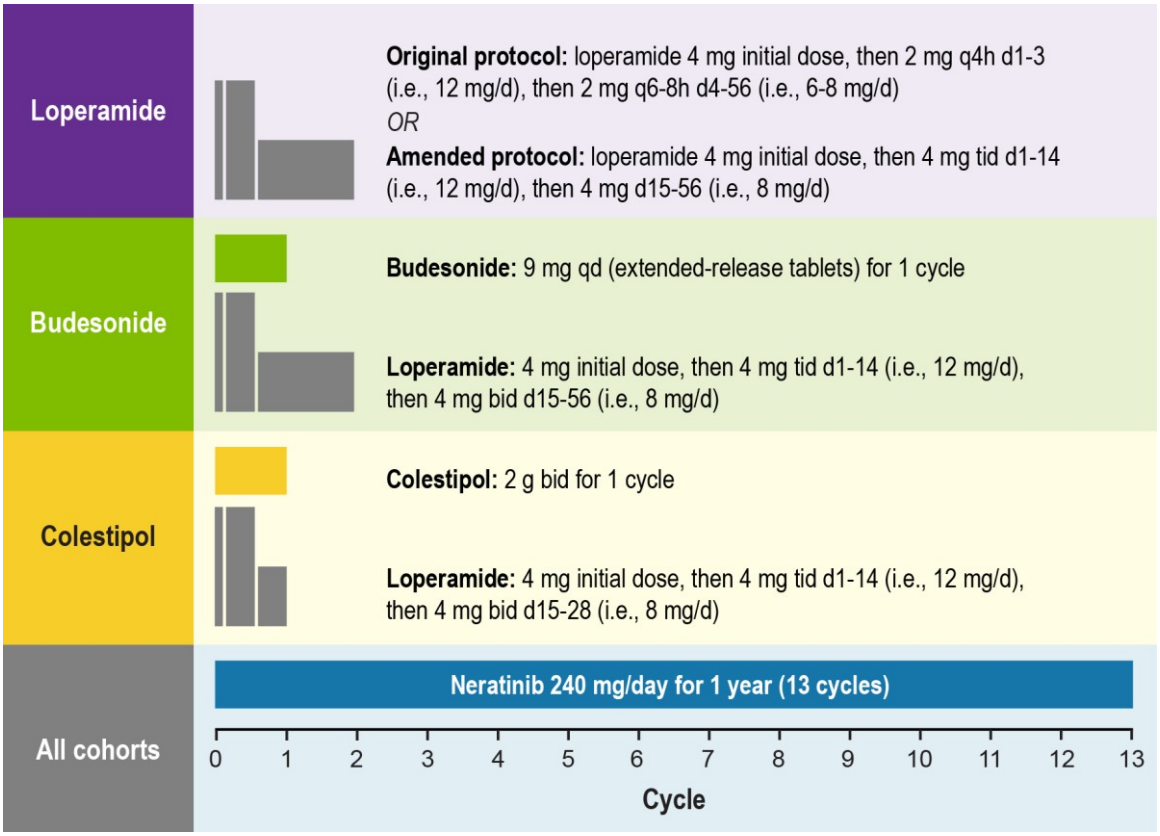
Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group; FACT-B, Functional Assessment of Cancer Therapy–Breast; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; LVEF, left ventricular ejection fraction; US, United States.

Sources: ClinicalTrials.gov (2018)[55]; Puma data on file (2016)[58]; Hurvitz et al. (2017)[50]

B.2.3.2.2 CONTROL: trial design and protocol amendments

Figure 3 presents the initial three cohorts of CONTROL that have completed recruitment and reported results, as described in Section B.2.6. All cohorts received neratinib with structured loperamide prophylaxis after prior treatment with trastuzumab. Separate patient cohorts were treated with budesonide (corticosteroid) or colestipol (bile acid sequestrant) in addition to loperamide to determine if these treatments could further reduce neratinib-associated diarrhoea.[50] Additional cohorts with structured dose escalations of neratinib or colestipol without structured loperamide prophylaxis are being recruited[55]; as these results are not yet available, these cohorts are not discussed further in this dossier. The ExteNET trial, which included an analogous patient population but no protocol-mandated antidiarrhoeal prophylaxis, was used as a reference point.[50]

Figure 3. CONTROL study flowchart (original cohorts)



Abbreviations: bid, twice daily; q4h, every 4 hours; q6-8h, every 6-8 hours; qd, once daily; tid, three times a day.

Note: One cycle = 28 days.

Source: Hurvitz et al. (2017)[50]

Neratinib treatment consisted of oral neratinib 240 mg once daily with food for 64 days or until disease recurrence (as determined by the investigator), death, unacceptable toxicity, or other specified withdrawal criterion. The neratinib dose could be reduced to 160 mg or 120 mg daily to manage toxicity. Once the neratinib dose was reduced for a patient, all subsequent cycles were to be administered at that dose, unless further dose reduction was required.[50]

Loperamide was the primary prophylaxis antidiarrhoeal medication mandated in CONTROL. Loperamide 4 mg (2 tablets/capsules) was taken three times daily during the first two 28-day cycles of neratinib treatment.

In the original protocol, an initial dose of loperamide 4 mg was administered on cycle 1/day 1 concomitantly with the first dose of neratinib. Subsequent 2 mg doses of loperamide were to be taken every 4 hours on days 1, 2, and 3 (for a total daily dose of 12 mg), and then every 6 to 8 hours (for a total daily dose of 6-8 mg) starting on day 4 until the end of the second cycle of therapy (day 56). Prophylaxis was continued in subsequent cycles at the discretion of the investigator.[50]

With Amendments 1 and 2, the loperamide dosing schedule was modified to simplify the regimen and to prevent or manage diarrhoea in initially enrolled patients. The amended regimen was as follows:

- For the first 14 days, loperamide 4 mg was self-administered orally by patients three times daily (for a total daily dose of 12 mg).
- Loperamide dose reduction guidelines for constipation were provided.

With Amendment 3, oral budesonide (9 mg daily) was added for cycle 1.

With Amendment 4, colestipol (2 g twice daily) was added for cycle 1.

Enrolment into additional cohorts is ongoing; the final analysis of the CONTROL study will be performed when all patients have completed 12 months of neratinib therapy.[50]

B.2.3.2.3 CONTROL: baseline characteristics

At the time of the database cutoff for the interim safety report (3 November 2017), the safety population consisted of 321 patients who had received at least one dose of neratinib as follows: loperamide cohort (n = 137), budesonide cohort (n = 64; still actively recruiting), and colestipol cohort (n = 120).[50]

0 presents baseline characteristics of CONTROL and the historic cohort of ExteNET. Baseline characteristics were similar in CONTROL and ExteNET; however, the following differences were noted: more CONTROL patients had HR+ tumours, more had received taxanes, and fewer had received anthracyclines, but more ExteNET patients had stage III tumours at diagnosis. In addition, 40% to 63% of patients in CONTROL, but none in ExteNET, had received pertuzumab as either neoadjuvant or adjuvant therapy. Finally, ExteNET included patients from Europe, South Africa, South America, and Asia Pacific, which were regions not represented in the original three cohorts of CONTROL.[50]

The safety population of CONTROL included all patients with early HER2+ breast cancer regardless of HR status, reflecting the ITT population of the ExteNET trial. However, the authorised marketing indication for neratinib (the label population) is narrower: patients with HR+/HER2+ breast cancer who have completed a course of adjuvant trastuzumab less than 1 year ago. Baseline demographic data show that most of the safety population of CONTROL had HR+/HER2+ breast cancer (72%-75%) and the median time since last trastuzumab dose in all cohorts was less than 4.3 months. In addition, patients with a median time since last trastuzumab dose of more than 12 months are considered protocol deviations for the entry criteria and will be removed from the final analysis.[50]

Table 10. Baseline characteristics for the interim analysis population for CONTROL

	CONTROL			ExteNET
Characteristic	**Loperamide cohort**	**Budesonide + loperamide cohort**	**Colestipol + loperamide cohort**	**Neratinib arm (loperamide as needed)**
N (at data cutoff[a])	137	64	120	1,420
Median age (range), years	53 (30-86)	49 (29-78)	53 (26-78)	52 (25-83)
Tumour stage at diagnosis, %				
I	28.5	25.0	16.7	9.8
IIA, IIB	54.7	46.9	46.7	42.0
IIIA, IIIB, IIIC	14.6	23.4	26.7	31.2
IV	0.7	0	0.8	0
Hormone receptor status, %				
Positive (ER+ and/or PR+)	75.2	71.9	72.5	57.5
Negative (ER– and PR–)	24.8	28.1	26.7	42.5
Prior (neo)adjuvant therapy, %				
Trastuzumab	99.3	96.9	99.2	100
Taxanes	95.6	96.9	98.3	77.3
Anthracycline	26.3	28.1	24.2	90.1
Pertuzumab	40.1	60.9	62.5	–
Median (range) duration of prior trastuzumab, months[b]	11.5 (2.4-18.2)	10.9 (9.8-11.6)	11.0 (10.0-11.8)	11.5 (0.7-56.9)
Median (range) time since last trastuzumab dose, months	3.9 (0.1-12.1)	4.3 (0.5-17.1)	2.7 (0.0-18.6)	4.4 (0.2-30.9)

Abbreviations: ER, oestrogen receptor; PR, progesterone receptor.

[a] Data cutoff: 3 November 2017.

[b] Patients with a median time since last trastuzumab dose > 12 months are considered protocol deviations for the entry criteria and will be removed from the final analysis.

Source: Hurvitz et al. (2017)[50]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 ExteNET

The primary objective of ExteNET was to compare iDFS in women with early-stage HER2-overexpressed/amplified breast cancer following trastuzumab in the adjuvant setting treated with neratinib versus placebo.[60]

The primary endpoint was iDFS—time from randomisation to the first occurrence of the following DFS events: invasive ipsilateral breast tumour recurrence, local/regional invasive recurrence, distant recurrence, death from any cause, or invasive contralateral breast cancer. For any patient for whom a DFS event was not

observed by the cutoff date of an analysis, DFS was censored at the date of the last physical examination (either scheduled or unscheduled).

Secondary endpoints included disease-free survival including ductal carcinoma in situ (DFS-DCIS), time to distant recurrence (TTDR), distant disease-free survival (DDFS), cumulative incidence of central nervous system (CNS) recurrences, OS, and safety. All time-to-event secondary endpoints were defined as from time of randomisation as follows[60]:

- *DFS-DCIS:* Time from randomisation to the first occurrence of a DFS event (as defined for the primary endpoint) or DCIS. DFS-DCIS events included DCIS and all DFS events. For patients who have a DCIS diagnosis followed by a DFS event, the date of event for DFS-DCIS was the date of DCIS.
- *TTDR:* Time between randomisation and the date of the first distant recurrence or death from breast cancer. TTDR events included distant recurrence and death from breast cancer.
- *DDFS:* Time from randomisation to the first occurrence of distant recurrence or death from any cause. DDFS events included distant recurrence and death from any cause.
- *Incidence of CNS recurrence:* Cumulative incidence of CNS recurrence as first distant recurrence (either isolated CNS metastases or diagnosed concurrently with other sites of metastatic disease).
- *OS:* Time from the date of randomisation until the date of death, censored at the last date known alive.
- Short- and long-term safety (including incidence of grade ≥ 3 diarrhoea).

Table 11 provides a summary of the planned statistical analyses in ExteNET.

Table 11. Summary of the statistical analyses of ExteNET

Study	ExteNET
Hypothesis objective	To compare iDFS of women with early-stage HER2-overexpressed/amplified breast cancer following trastuzumab in the adjuvant setting who are receiving neratinib versus placebo
Statistical analysis	Time-to-event endpoints were tested with 2-sided log-rank tests, either unstratified (label population) or stratified[a] by randomisation factors (intention-to-treat population), and unstratified or stratified[a] Cox proportional hazards models were used to estimate hazard ratios with 95% CIs. Kaplan-Meier methods were used to estimate 2-year survival rates. Cumulative incidence in competing-risk analysis was done for CNS recurrences, and Gray's test was used to compare treatments. Adverse events were graded according to the National Cancer Institute *Common Terminology Criteria*, version 3.0. Changes from baseline in quality of life scores were compared with ANCOVA, with baseline score as a covariate.
Sample size, power calculation	The study was originally designed to enrol 3,850 patients, with a 90% power to detect a hazard ratio of 0.7 for iDFS at a 2-sided 5% significance level. In October 2011, enrolment was stopped after 2,842 patients were randomly assigned, and follow-up was truncated at 2 years. Consequently, the 2-year analysis of iDFS was considered to be the primary analysis; the study was expected to have 241 iDFS events; and the power was projected to be 88%, based on a one-sided log-rank test with a type 1 error of 0.025. No interim analyses were planned owing to cessation of recruitment.
Data management and patient withdrawals	Any patient for whom an event had not been observed by the data cutoff was censored at the date of their last physical examination.
Missing data	The primary analyses did not impute missing values. Patients missing baseline assessments for FACT-B and EQ-5D questionnaires were not included in the analysis of the health outcomes assessments. Partial dates for adverse events: ▪ If the start day was missing, the date was imputed as the first day of the month ▪ If the end day was missing, the date was imputed as the last day of the month. If the month, year, both month and year, or the entire date was missing, then no data imputation was implemented; these events were counted with regard to frequency, but the duration was defined as unknown.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CNS, central nervous system; FACT-B, Functional Assessment of Cancer Therapy–Breast; HER2, human epidermal growth factor receptor 2; iDFS, invasive disease-free survival.

[a] Although an unstratified analysis was stated in the protocol, it was revised to a stratified analysis in the statistical analysis plan before unmasking, so that the primary analysis was consistent with the stratified design of the trial.

Sources: Puma data on file (2016)[61]; Chan et al. (2016)[48]

Two efficacy analyses were planned at 2 and 5 years after randomisation[60]:

- Primary analysis: 2-year follow-up analyses to assess the efficacy study data collected during the 2-year follow-up period initiated under Amendment 9
- Sensitivity analysis: 5-year follow-up analyses to assess durability of the treatment effect on iDFS and the impact of OS using the efficacy study data collected during the 5-year follow-up period initiated under Amendment 13

Approximately 75% of patients were reconsented for extended follow-up beyond 24 months. Observations with missing data were censored at the last date of assessment.

The following four prespecified analysis populations were included[60]:

- ITT population (primary): all patients randomised into the study
- Amended ITT population: randomised under Amendment 3 or subsequent amendments; randomised before implementation of Amendment 3 if they had node-positive disease and randomisation within 1 year from completion of prior trastuzumab therapy
- Centrally confirmed HER2+ population: all patients randomised who were confirmed by central testing
- Safety population: all patients who received at least one dose of study drug

Prespecified subgroup analyses included the following[60]:

- ER/PR status (positive or negative)
- Nodal status (negative vs. 1-3 vs. 4 or more)
- Trastuzumab given sequentially or concurrently with chemotherapy
- Patients who completed prior trastuzumab ≤ 1 year or > 1 year from randomisation

The efficacy endpoints assessed for the subgroups included iDFS, DFS-DCIS, TTDR, and DDFS. The incidence of CNS recurrence was not included in the subgroup analysis because there were insufficient events for meaningful statistical analysis. For any patient for whom a DFS-DCIS or TTDR or DDFS event was not observed by the cutoff date of an analysis, data were censored at the date of the last physical examination. For TTDR, if the patient died of causes other than breast cancer, the TTDR was censored at the date of death.

An additional subgroup analysis was requested by the European Medicines Agency for HR+ patients who were within 1 year of completion of trastuzumab therapy. Although this subgroup was not explicitly defined in the statistical analysis plan, both variables used to define the label population of interest (i.e., HR status and ≤ 1 year from completion of prior trastuzumab-based therapy) were prespecified individually in the statistical analysis plan.[52]

The ExteNET efficacy results presented here are based on the 2-year and 5-year results for the ITT population[47,48] and the label population that is relevant to the NICE decision problem (people with HR+/HER2+ breast cancer within 1 year of completion of trastuzumab therapy).[52] Mature OS results are pending; however, OS data for the

HR+ subset will only be available from [redacted], and the sponsor/Puma remains blinded until then.

Safety analyses were done in the safety population, defined as all patients who received at least one dose of study treatment. Adverse events were graded according to the National Cancer Institute *Common Terminology Criteria* (NCI-CTC), version 3.0.[48]

For the primary HRQoL analysis, evaluable patients were required to have a baseline HRQoL assessment and at least one postbaseline HRQoL assessment. Changes from baseline were compared between treatment groups at each time point using a prespecified analysis of covariance (ANCOVA) with baseline score as a covariate and no imputation for missing values. Adjusted least squares mean values with 95% CIs were estimated within treatment groups and for differences between treatment groups at each time point. A prespecified secondary analysis was performed using a mixed-effect model that included visit and treatment as covariates. The model incorporated all available data and assumed that any missing postbaseline observations were missing at random.[54]

B.2.4.2 CONTROL

The primary objective of CONTROL is to characterise the duration, incidence and severity of diarrhoea in patients with early-stage HER2+ breast cancer treated with neratinib when administered with structured antidiarrhoeal strategies after prior treatment with trastuzumab.[50,58]

The primary endpoint of CONTROL is the incidence of grade ≥ 3 diarrhoea during treatment with neratinib at any time during the study. Secondary and exploratory endpoints are as follows:

- To evaluate the association between antidiarrhoeal treatment exposure and incidence and severity of diarrhoea, such as loperamide with and without anti-inflammatory agents, or with and without a bile acid sequestrant
- To assess the incidence of serious adverse events (SAEs) and other adverse events (AEs) of special interest
- Patient-reported HRQoL (exploratory endpoint)

As the objective of CONTROL is to provide additional safety data for neratinib, the results presented in Section B.2.6.2 of this submission are for the entire safety analysis set for CONTROL (i.e., all patients who received neratinib), which includes all patients with early HER2+ breast cancer, regardless of HR status.

Table 12 provides a summary of the planned statistical analyses in CONTROL. All safety analyses were descriptive and performed in the safety population (all patients

who received ≥ 1 neratinib dose). Adverse events were graded according to National Cancer Institute *Common Terminology Criteria for Adverse Events* (NCI-CTCAE) (version 4.0). HRQoL analyses were descriptive and performed in the QoL analysis population (all patients in the safety population with baseline and ≥ 1 postbaseline QoL assessment). Mean (standard error) observed HRQoL scores over time were calculated. The primary analyses did not impute missing values. Changes in HRQoL scores from baseline, if greater than the previously reported lowest estimate for an important difference, were considered clinically meaningful. The ExteNET trial, which included an analogous patient population but no protocol-mandated antidiarrhoeal prophylaxis, was used as an historical control.[50]

Table 12. Summary of the statistical analyses of CONTROL

Study	CONTROL
Hypothesis objective	To characterise diarrhoea incidence and severity in patients treated with neratinib plus structured antidiarrhoeal prophylaxis (such as loperamide with or without budesonide or colestipol) compared with neratinib plus loperamide as needed
Statistical analysis	2-sided 95% Clopper-Pearson CIs will be computed. All safety analyses were descriptive and performed in the safety population (all patients who received ≥ 1 neratinib dose). AEs were graded according to National Cancer Institute C*ommon Terminology Criteria for Adverse Events* (version 4.0). HRQoL analyses were descriptive and performed in the QoL analysis population (all patients in the safety population with baseline and ≥ 1 postbaseline QoL assessment). Mean (standard error) observed HRQoL scores over time were calculated.
Sample size, power calculation	The incidence of grade ≥ 3 diarrhoea is assumed to be 15% in this study. A sample size of 120 patients will ensure that the width of the 95% CI of the incidence of grade ≥ 3 diarrhoea is no more than 18.5%. For example, if 18 of 120 patients are observed to have grade ≥ 3 diarrhoea, the incidence and its 95% (2-sided) CIs will be 15.0% (9.1%-22.7%), in which the width of the CI is 13.5%. In addition to the analyses of the overall safety population, antidiarrhoeal prophylaxis regimen–specific subgroup analyses will be performed as needed. Precision of the estimated 95% CIs for the regimen-specific subgroup(s) will be lower than what is provided above for the overall safety population. Starting with Amendment 3, the effect of anti-inflammatory treatments on the incidence, severity, and duration of diarrhoea will be assessed. Starting with Amendment 4, the effect of a bile acid sequestrant will be assessed. A sample size of 40 patients will ensure that the width of the 95% CI of the incidence of grade ≥ 3 diarrhoea is no more than 33%. For example, if 4 of 40 patients are observed to have grade ≥ 3 diarrhoea, the incidence and its 95% (2-sided) CI will be 10.0% (2.8%-23.7%), in which the width of the CI is 21%.
Data management and patient withdrawals	In all cases, the reason(s) for premature discontinuation/withdrawal, and the primary reason, must be recorded on the CRF. If a patient is prematurely withdrawn from the investigational product or the study for any reason, the investigator must make every effort to perform the evaluations described for the EOT visit (performed within 5 days of the last dose of investigational product as appropriate). If a patient discontinues because of an AE, the patient should be strongly encouraged to undergo the EOT assessments and continue to be under medical supervision until symptoms cease or the condition becomes stable. If a patient is lost to follow-up or voluntarily withdraws from study participation, every effort should be made to determine why a patient is lost to follow-up or withdraws consent. This information, including the date, should also be recorded on the patient's conclusion of patient participation CRF. All patients will remain on active study treatment until a cause of early treatment discontinuation occurs. These include disease progression, unacceptable toxicity, and withdrawal of consent or until study closure.
Missing data	The primary analyses did not impute missing values.

Abbreviations: AE, adverse event; CI, confidence interval; CRF, case report form; EOT, end of treatment; HRQoL, health-related quality of life; QoL, quality of life.

Sources: Puma data on file (2016)[58]; Hurvitz et al. (2017)[50]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table 13 and Table 14 summarise the quality assessments carried out for ExteNET; additional detail is provided in Appendix D.

Table 13. Quality assessment of ExteNET (NCT00878709)

Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in dropouts between groups?	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an ITT analysis? **If so, was this appropriate and were appropriate methods used to account for missing data?**	Yes
Did the authors of the study publication declare any conflicts of interest?	Yes
Does the trial reflect routine clinical practice in England?	Yes

Abbreviation: ITT, intention to treat.

Sources: Quality assessment based on NICE (2015)[67]; Chan et al. (2016)[48]; Martin et al. (2017)[47]

Table 14. CASP quality assessment of CONTROL (NCT02400476)

1. Did the study address a clearly focused issue?	Yes
2. Did the authors use an appropriate method to answer their question?	No
3. Was the cohort recruited in an acceptable way?	Unclear
4. Was the exposure accurately measured to minimise bias?	Yes
5. Was the outcome accurately measured to minimise bias?	Yes
6A. Have the authors identified all important confounding factors?	Yes
6B. Have they taken account of the confounding factors in the design and/or analysis?	Yes
7A. Was the follow-up of subjects complete enough?	Yes/unclear

7B. Was the follow-up of subjects long enough?	Yes/unclear
8. What are the results of this study?	A structured loperamide prophylactic regimen for 1 or 2 cycles, with or without the addition of either budesonide or colestipol for a single cycle, reduces the incidence, severity, and duration of neratinib-associated diarrhoea compared with that observed in the ExteNET trial. Incidence of grade ≥ 3 diarrhoea was as follows: loperamide, 30.7% (95% CI, 23.1%-39.1%); loperamide with budesonide, 26.6% (95% CI, 16.3%-39.1%); loperamide with colestipol, 10.8% (95% CI, 5.9%-17.8%); ExteNET historical control, 39.9% (95% CI, 37.3%-42.5%). Any HRQoL impairment is short-lived and does not reach predefined clinically meaningful thresholds in the loperamide cohort. However, the small sample size and lack of within-study comparator arm limit the conclusions that can be drawn from these data.
9. How precise are the results?	95% CIs are used throughout.
10. Do you believe the results?	Yes
11. Can the results be applied to the local population?	Yes
12. Do the results of this study fit with other available evidence?	Unclear
Did the authors of the study publication declare any conflicts of interest?	Unclear
Does the trial reflect routine clinical practice in England?	Unclear

Abbreviations: CASP, Critical Appraisal Skills Programme; CI, confidence interval; HRQoL, health-related quality of life.

Sources: Quality assessment based on CASP (2018)[68]; Hurvitz et al. (2017)[50]; Ibrahim et al. (2017)[49]

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 ExteNET

B.2.6.1.1 ExteNET: clinical effectiveness

As described in Section B.2.3, efficacy data presented in this section include results of analyses from the label population relevant to the NICE decision problem (patients with early HR+/HER2+ breast cancer within 1 year of trastuzumab therapy) and the entire ITT population for ExteNET (all patients randomised regardless of HR status or time from completion of trastuzumab). For the label population, unstratified hazard ratios as specified in the protocol and included in the label are presented[1] as well as additional analyses from published reports, including stratified hazard ratios for the ITT population to reflect the stratified trial design.[47,48,69] HRQoL data from ExteNET are for all evaluable ITT participants who completed HRQoL questionnaires at baseline and at least one postbaseline visit, regardless of HR status or time from completion of trastuzumab therapy.[53,54]

The 2-year primary analysis was conducted in July 2014. The median duration of treatment was 353 days (range, 1-406 days) in the neratinib group and 360 days (range, 4-401 days) in the placebo group. Median relative dose intensity was 82% (range, 0.3%-105.5%) in the neratinib group and 98% (range, 1.1%-108.5%) in the placebo group. Median follow-up was 24 months (IQR, 20-25) in the neratinib group and 24 months (IQR, 22-25) in the placebo group.[48]

The 5-year analysis was done in March 2017. At the cutoff date of 1 March 2017, 2,117 (75%) patients had reconsented to retrospective data collection between years 2 and 5 and survival data beyond year 5 (neratinib group, n = 1,028; placebo group, n = 1,089). Baseline characteristics were similar between treatment groups in patients who reconsented and between the ITT and reconsented populations. The median duration of treatment was 353 days (IQR, 76-363 days) with neratinib and 360 days (IQR, 350-365 days) with placebo.[47]

Table 15, Table 16, and Figure 4 present summaries of the 2-year and 5-year efficacy analyses for the label and ITT populations; detailed results for each endpoint are described in the sections below.

Table 15. ExteNET: 2-year primary efficacy analyses for the label and ITT populations

Variable	Label population: HR+ population who are within 1 year of completion of trastuzumab			
	Estimated 2-year event-free rates[a] (%)		Hazard ratio (95% CI)[b]	*P* value[c]
	Neratinib (n = 670)	Placebo (n = 664)		
iDFS	95.3	90.8	0.49 (0.30-0.78)	0.002
DFS-DCIS	95.3	90.0	0.45 (0.28-0.71)	< 0.001
DDFS	96.1	92.9	0.53 (0.31-0.88)	0.015
TTDR	96.3	93.3	0.53 (0.30-0.89)	0.017
CNS recurrence	0.34	1.01	–	0.187

	ITT population			
	Estimated 2-year event-free rates[a] (%)			
	Neratinib (n = 1,420)	Placebo (n = 1,420)	Hazard ratio (95% CI)[d]	*P* value[e]
iDFS	94.2	91.9	0.66 (0.49-0.90)	0.008
DFS-DCIS	94.2	91.3	0.61 (0.45-0.83)	0.001
DDFS	95.3	94.0	0.74 (0.52-1.05)	0.094
TTDR	95.5	94.2	0.73 (0.51-1.04)	0.087
CNS recurrence	0.92	1.16	–	0.548

Abbreviations: CI, confidence interval; CNS, central nervous system; DDFS, distant disease-free survival; DFS-DCIS, disease-free survival including ductal carcinoma in situ; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; ITT, intention to treat; TTDR, time to distant recurrence.

[a] Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported.

[b] Unstratified Cox proportional hazards model.

[c] Unstratified 2-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.

[d] Stratified Cox proportional hazards model used for the ITT population.

[e] Stratified 2-sided log-rank test for all endpoints for the ITT population, except for CNS recurrence for which Gray's method was used.

Sources: NERLYNX® SmPC (2018)[1]; Gnant et al. (2018)[52]

Table 16. ExteNET: 5-year efficacy analyses for the label and ITT populations

Variable	Label population: HR+ population who are within 1 year of completion of trastuzumab			
	Estimated 5-year event-free rates[a] (%)		Hazard ratio (95% CI)[b]	*P* value[c]
	Neratinib (n = 670)	Placebo (n = 664)		
iDFS	90.8	85.7	0.58 (0.41-0.82)	0.002
DFS-DCIS	90.6	84.8	0.55 (0.39-0.77)	< 0.001
DDFS	92.4	87.7	0.57 (0.39-0.83)	0.003
TTDR	92.6	88.2	0.58 (0.39-0.85)	0.005
CNS recurrence	0.69	2.09	–	0.055
	ITT population			
	Estimated 5-year event-free rates[a] (%)		Hazard ratio (95% CI)[d]	*P* value[e]
	Neratinib (n = 1,420)	Placebo (n = 1,420)		
iDFS	90.2	87.7	0.73 (0.57-0.92)	0.0083
DFS-DCIS	89.7	86.8	0.71 (0.56-0.89)	0.0035
DDFS	91.6	89.9	0.78 (0.60-1.01)	0.065
TTDR	91.8	90.3	0.79 (0.60-1.03)	0.078
CNS recurrence	1.30	1.82	–	0.333

Abbreviations: CI, confidence interval; CNS, central nervous system; DDFS, distant disease-free survival; DFS-DCIS, disease-free survival including ductal carcinoma in situ; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; ITT, intention to treat; TTDR, time to distant recurrence.

[a] Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported.

[b] Unstratified Cox proportional hazards model.

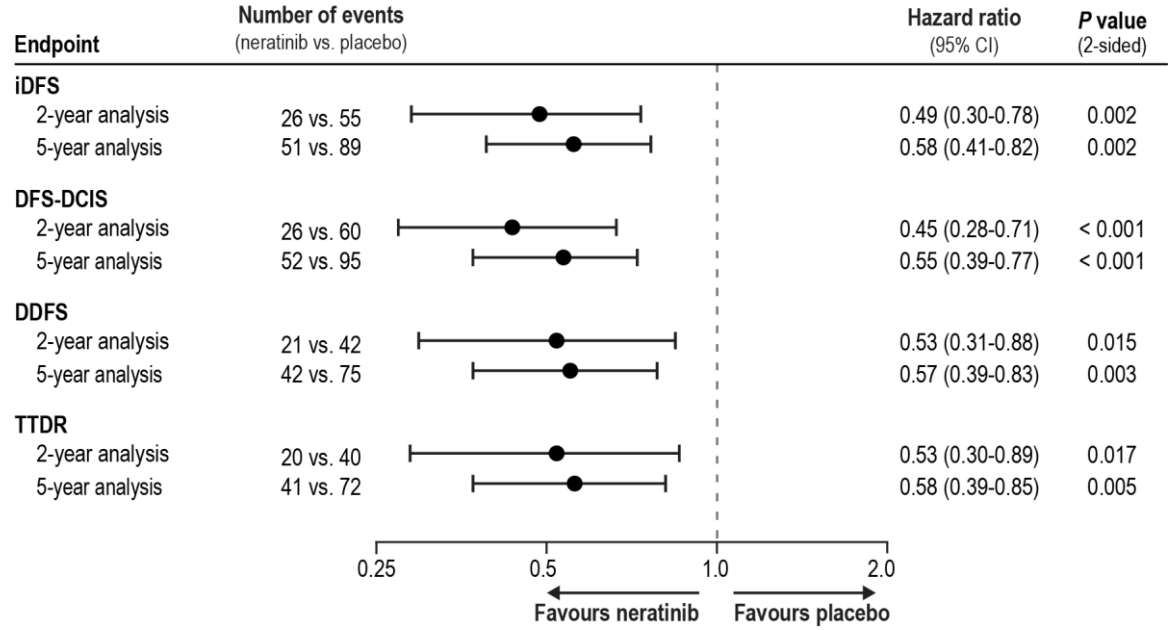
[c] Unstratified 2-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.

[d] Stratified Cox proportional hazards model.

[e] Stratified 2-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.

Sources: Puma data on file (2018)[69]; Gnant et al. (2018)[52]; Martin et al. (2017)[47]; Puma data on file (2018)[70]

Figure 4. ExteNET: forest plot of efficacy outcomes in patients with HR+/HER2+ tumours who are ≤ 1 year from the last dose of trastuzumab to randomisation (n = 1,334)



Abbreviations: CI, confidence interval; DDFS, distant disease-free survival; DFS-DCIS, disease-free survival including ductal carcinoma in situ; HER2+, human epidermal growth factor receptor 2-positive; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; TTDR, time to distant recurrence.

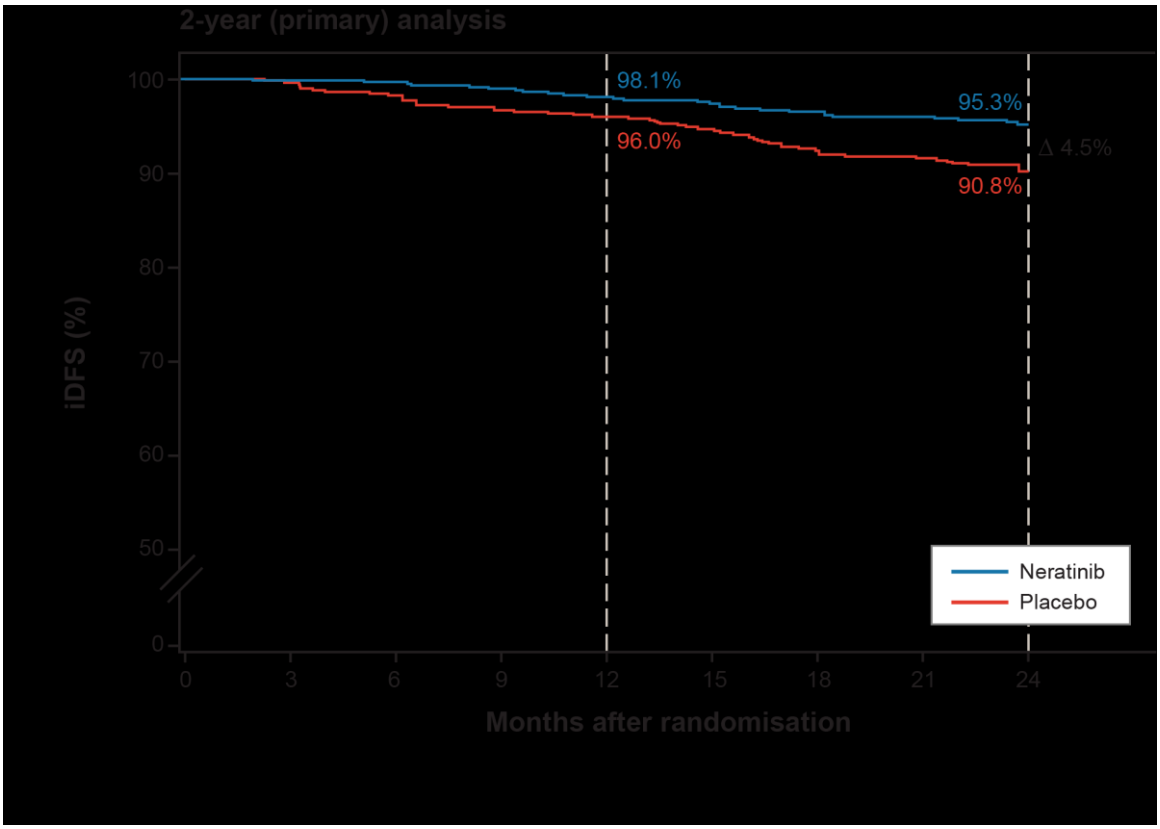
Source: Gnant et al. (2018)[52]

B.2.6.1.2 ExteNET primary endpoint: invasive disease-free survival

2-Year invasive disease-free survival

In the label population (n = 1,334), the 2-year iDFS rate was 95.3% for neratinib (n = 670) and 90.8% for placebo (n = 664), equating to an absolute benefit of 4.5% and a significant relative risk reduction of invasive disease recurrence or death by 51% versus placebo (26 vs. 55 events; unstratified hazard ratio, 0.49; 95% CI, 0.30-0.78; two-sided *P* = 0.002) (Figure 5).[1] Table 17 summarises iDFS events by site of first occurrence at 2 years.[71]

Figure 5. ExteNET: Kaplan-Meier curve of iDFS at 2 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab



Abbreviations: CI, confidence interval; HR+, hormone receptor-positive; iDFS, invasive disease-free survival.

Sources: NERLYNX® SmPC (2018)[1]; Gnant et al. (2018)[52]

Table 17. ExteNET: iDFS events at 2 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab

	Neratinib (n = 670)	**Placebo (n = 664)**
Patients with events, n (%)	26 (3.9)	55 (8.3)
Local/regional invasive recurrence	3 (0.4)	12 (1.8)
Invasive ipsilateral breast tumour recurrence	1 (0.1)	2 (0.3)
Invasive contralateral breast cancer	1 (0.1)	2 (0.3)
Distant recurrence	20 (3.0)	38 (5.7)
Death from any cause	1 (0.1)	1 (0.2)
Patients censored, n (%)	644 (96.1)	609 (91.7)
Kaplan-Meier estimate, % (95% CI)		
12 Months	98.1 (96.7-99.0)	96.0 (94.2-97.3)
24 Months	95.3 (93.1-96.7)	90.8 (88.2-92.9)
Stratified log-rank test *P* value (2-sided)[a]	0.003	
Unstratified log-rank test *P* value (2-sided)	0.002	
Stratified Cox proportional hazards model[a]		
Hazard ratio (95% CI)[b]	0.50 (0.31-0.79)	

	Neratinib (n = 670)	Placebo (n = 664)
Unstratified Cox proportional hazards model		
Hazard ratio (95% CI)[b]	0.49 (0.30-0.78)	

Abbreviations: CI, confidence interval; HR+, hormone receptor-positive; iDFS, invasive disease-free survival.

Note: Disease-free survival time is defined as the time from date of randomisation until the first disease recurrence of one of the following events: local/regional invasive recurrence, invasive ipsilateral breast tumour recurrence, invasive contralateral breast cancer, distant recurrence, or death from any cause.

[a] The log-rank test and Cox model are stratified by randomisation stratification factors: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4).

[b] The hazard ratio is presented as neratinib vs. placebo.

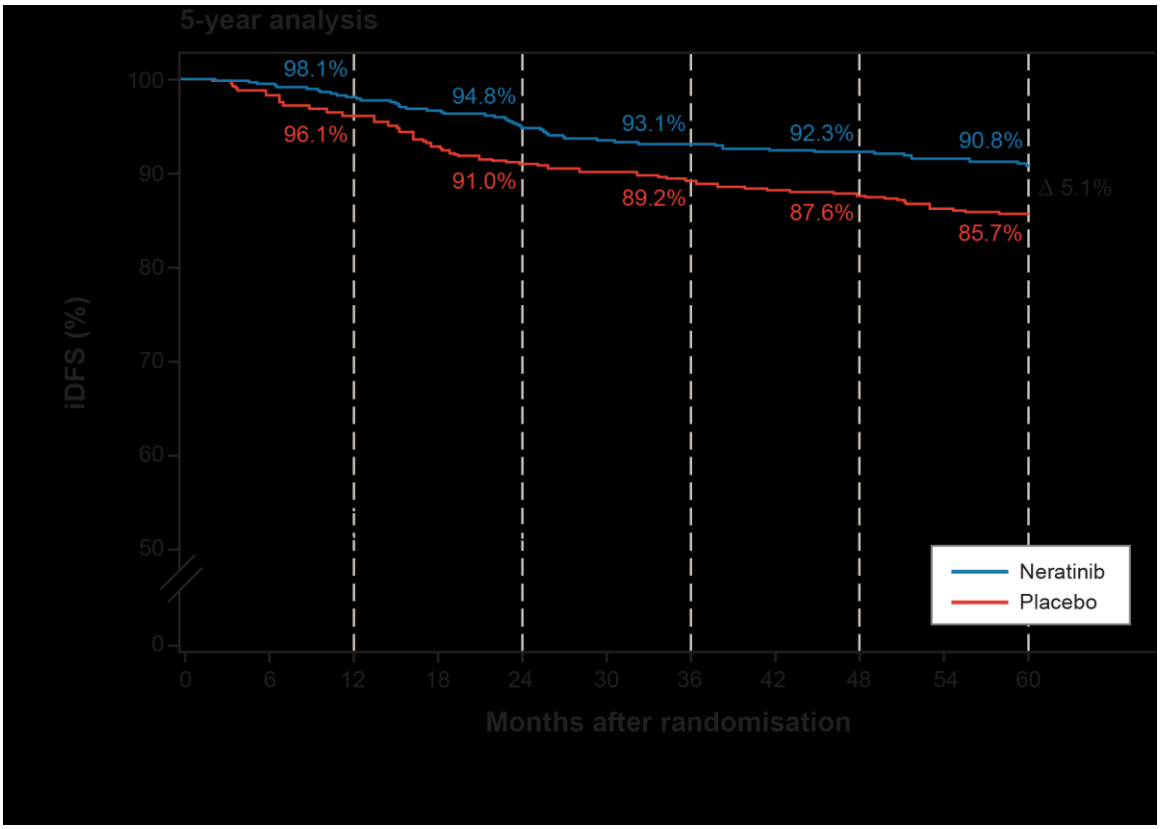
Source: Puma data on file (2018)[71]

For the ITT population (n = 2,840), 2-year iDFS rates were 94.2% for neratinib and 91.9% for placebo, with neratinib significantly reducing the risk of invasive disease recurrence or death by 34% versus placebo (70 vs. 109 events; stratified hazard ratio, 0.66; 95% CI, 0.49-0.90; two-sided $P = 0.008$).[1]

5-Year invasive disease-free survival

The treatment effect of neratinib over placebo was durable at 5 years postrandomisation. In the label population, the 5-year iDFS rate was 90.8% for neratinib (n = 670) and 85.7% for placebo (n = 664), equating to an absolute benefit of 5.1% and a significant relative risk reduction of invasive disease recurrence or death by 42% versus placebo (51 vs. 89 events; unstratified hazard ratio, 0.58; 95% CI, 0.41-0.82; two-sided $P = 0.002$). Kaplan-Meier curves for iDFS separated after approximately 3 months and remained separate for the rest of the 5-year follow-up (Figure 6).[52] Table 18 summarises iDFS events by site of first occurrence at 5 years.[72]

Figure 6. ExteNET: Kaplan-Meier curve of iDFS at 5 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab



Abbreviations: CI, confidence interval; HR+, hormone receptor-positive; iDFS, invasive disease-free survival.

Source: Gnant et al. (2018)[52]

Table 18. ExteNET: iDFS events at 5 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab

	Neratinib (n = 670)	**Placebo (n = 664)**
Patients with events, n (%)	51 (7.6)	89 (13.4)
Local/regional invasive recurrence	5 (0.7)	18 (2.7)
Invasive ipsilateral breast tumour recurrence	2 (0.3)	5 (0.8)
Invasive contralateral breast cancer	2 (0.3)	5 (0.8)
Distant recurrence	40 (6.0)	63 (9.5)
Death from any cause	2 (0.3)	3 (0.5)
Patients censored, n (%)	619 (92.4)	575 (86.6)
Kaplan-Meier estimate, % (95% CI)		
12 Months	98.1 (96.6-98.9)	96.1 (94.3-97.4)
24 Months	94.8 (92.7-96.3)	91.0 (88.5-93.0)
36 Months	93.1 (90.7-94.9)	89.2 (86.4-91.4)
48 Months	92.3 (89.7-94.2)	87.6 (84.7-90.0)
60 Months	90.8 (88.1-93.0)	85.7 (82.6-88.3)
Stratified log-rank test *P* value (2-sided)[a]	0.002	

	Neratinib (n = 670)	Placebo (n = 664)
Unstratified log-rank test *P* value (2-sided)	0.002	
Stratified Cox proportional hazards model[a]		
Hazard ratio (95% CI)[b]	0.59 (0.41-0.82)	
Unstratified Cox proportional hazards model		
Hazard ratio (95% CI)[b]	0.58 (0.41-0.82)	

Abbreviations: CI, confidence interval; HR+, hormone receptor-positive; iDFS, invasive disease-free survival.

Note: Disease-free survival time is defined as the time from date of randomisation until the first disease recurrence of one of the following events: local/regional invasive recurrence, invasive ipsilateral breast tumour recurrence, invasive contralateral breast cancer, distant recurrence, or death from any cause.

[a] The log-rank test and Cox model are stratified by randomisation stratification factors: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4).

[b] The hazard ratio is presented as neratinib vs. placebo.

Source: Puma data on file (2018)[72]

Five-year data for the ITT population also demonstrated the durability of the treatment effect of neratinib versus placebo. Five-year iDFS rates were 90.2% for neratinib and 87.7% for placebo, with neratinib significantly reducing the risk of invasive disease recurrence or death by 34% versus placebo (stratified hazard ratio, 0.73; 95% CI, 0.57-0.92; two-sided $P = 0.0083$).[47] After 5 years in the ITT population, patients in the neratinib group had significantly fewer iDFS events than in the placebo group (116 vs. 163 events; two-sided $P = 0.008$).[47]

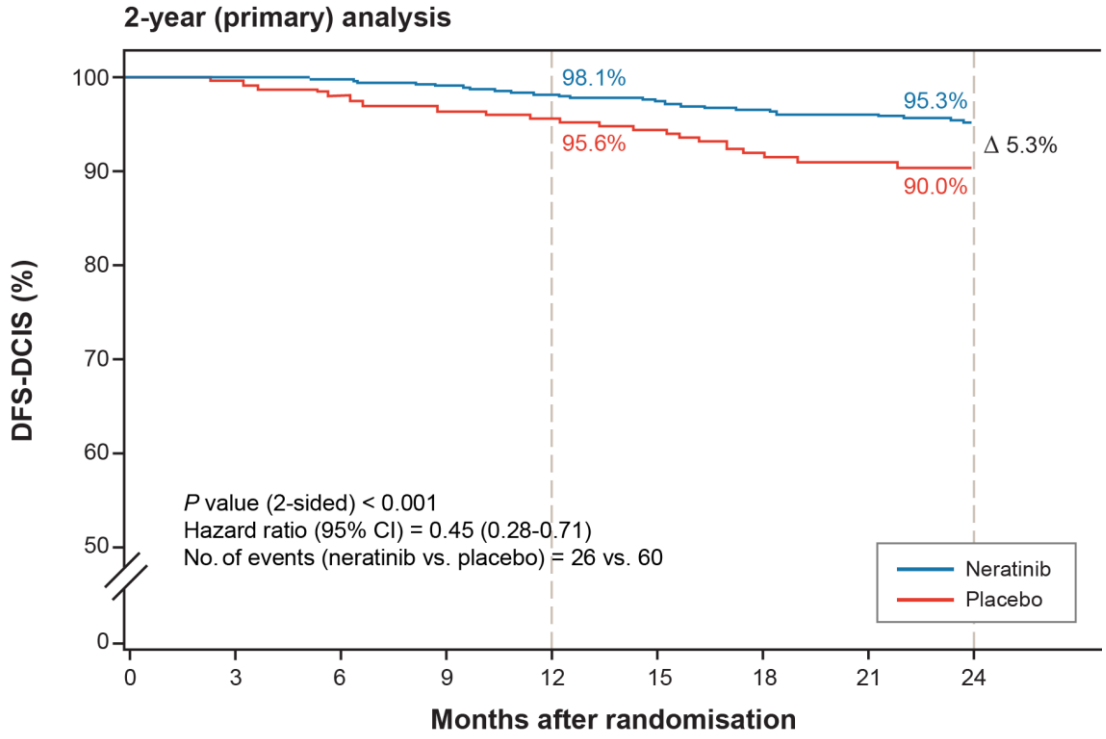
B.2.6.1.3 ExteNET secondary efficacy endpoints

Disease-free survival including ductal carcinoma in situ

A similar treatment effect was seen with neratinib when DCIS was included in the DFS analysis. DFS-DCIS was significantly improved in the neratinib group versus placebo, at both 2 and 5 years after randomisation in all analyses.

In the label population (n = 1,334), the 2-year DFS-DCIS rate was 95.3% for neratinib (n = 670) and 90.0% for placebo (n = 664), equating to an absolute benefit of 5.3% and a significant relative risk reduction of disease recurrence or death by 55% versus placebo (26 vs. 60 events; unstratified hazard ratio, 0.45; 95% CI, 0.28-0.71; two-sided $P < 0.001$) (Figure 7).[1,52]

Figure 7. ExteNET: Kaplan-Meier curve of DFS-DCIS at 2 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab



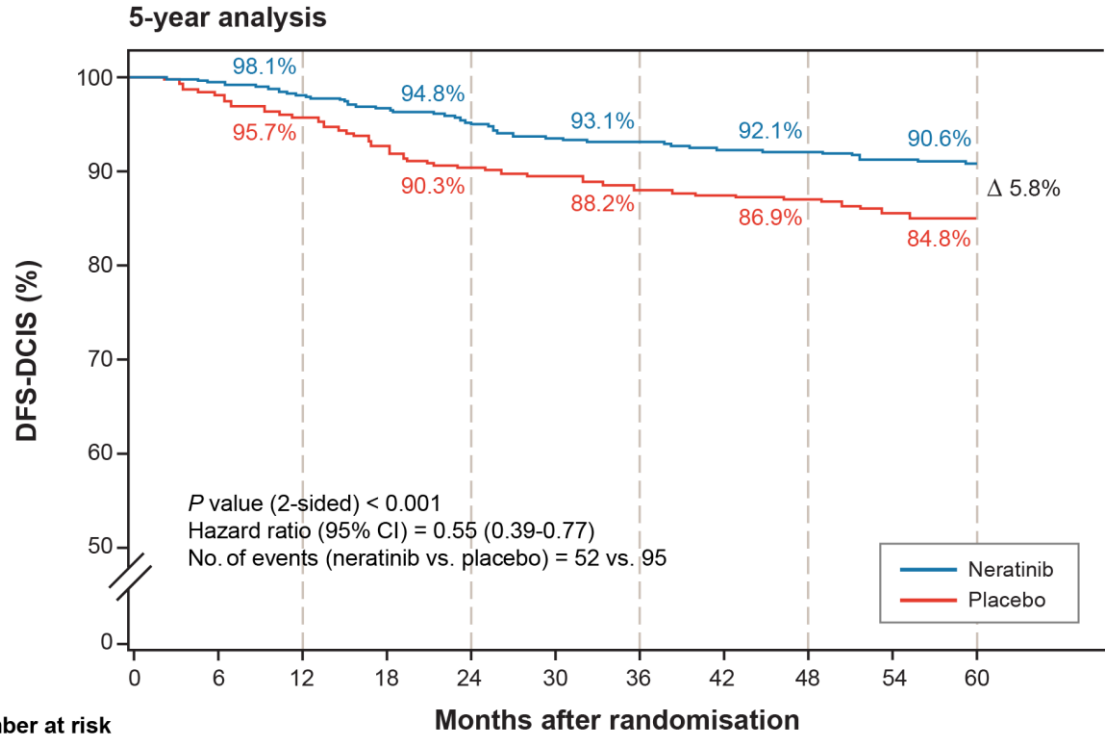
Abbreviations: CI, confidence interval; DFS-DCIS, disease-free survival including ductal carcinoma in situ; HR+, hormone receptor-positive.

Source: Puma data on file (2018)[73]

For the ITT population (n = 2,840), 2-year DFS-DCIS rates were 94.2% for neratinib and 91.3% for placebo, with neratinib significantly reducing the risk of disease recurrence or death by 39% versus placebo (stratified hazard ratio, 0.61; 95% CI, 0.45-0.83; two-sided *P* = 0.001).[1]

In the label population, the 5-year DFS-DCIS rate was 90.6% for neratinib (n = 670) and 84.8% for placebo (n = 664), equating to an absolute benefit of 5.8% and a significant relative risk reduction of 45% versus placebo (52 vs. 95 events; unstratified hazard ratio, 0.55; 95% CI, 0.39-0.77; two-sided *P* < 0.001) (Figure 8).[52]

Figure 8. ExteNET: Kaplan-Meier curve of DFS-DCIS at 5 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab



Number at risk

HR+/≤ 1 year from trastuzumab											
Neratinib	670	620	599	577	523	469	465	459	456	447	427
Placebo	664	633	608	581	533	479	468	460	456	448	430

Abbreviations: CI, confidence interval; DFS-DCIS, disease-free survival including ductal carcinoma in situ; HR+, hormone receptor-positive.

Source: Puma data on file (2018)[74]

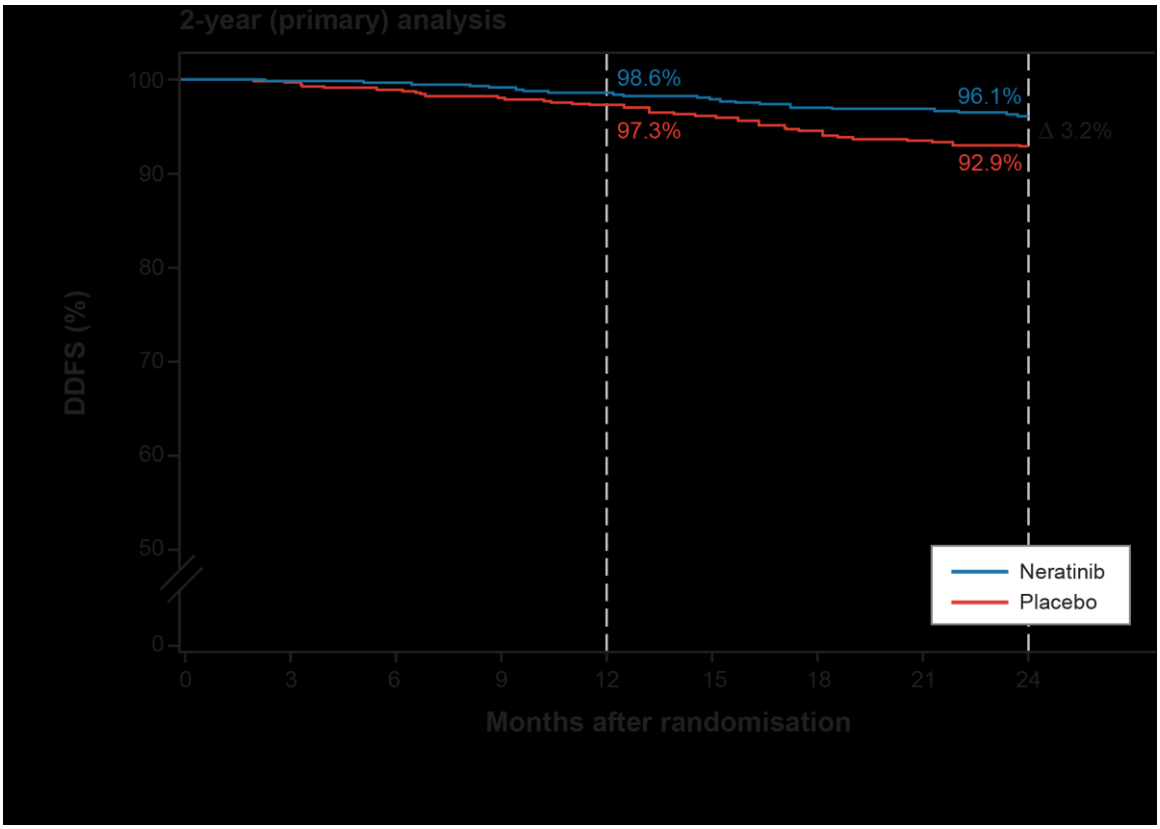
In the ITT population, 5-year DFS-DCIS rates were 89.7% for neratinib and 86.8% for placebo, with neratinib significantly reducing the risk of disease recurrence or death by % versus placebo (stratified hazard ratio, 0.71; 95% CI, 0.56-0.89; two-sided *P* = 0.0035).[47]

Distant disease-free survival

There was a significant difference between treatment groups in DDFS at 2 years and 5 years after randomisation in the label population but not in the ITT population at either 2 or 5 years postrandomisation.

In the label population (n = 1,334), the 2-year DDFS rate was 96.1% for neratinib (n = 670) and 92.9% for placebo (n = 664), equating to an absolute benefit of 3.2% and a significant relative risk reduction of distant disease recurrence or death of 47% versus placebo (21 vs. 42 events; unstratified hazard ratio, 0.53; 95% CI, 0.31-0.88; two-sided *P* = 0.015) (Figure 9).[1,52]

Figure 9. ExteNET: Kaplan-Meier curve of DDFS at 2 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab



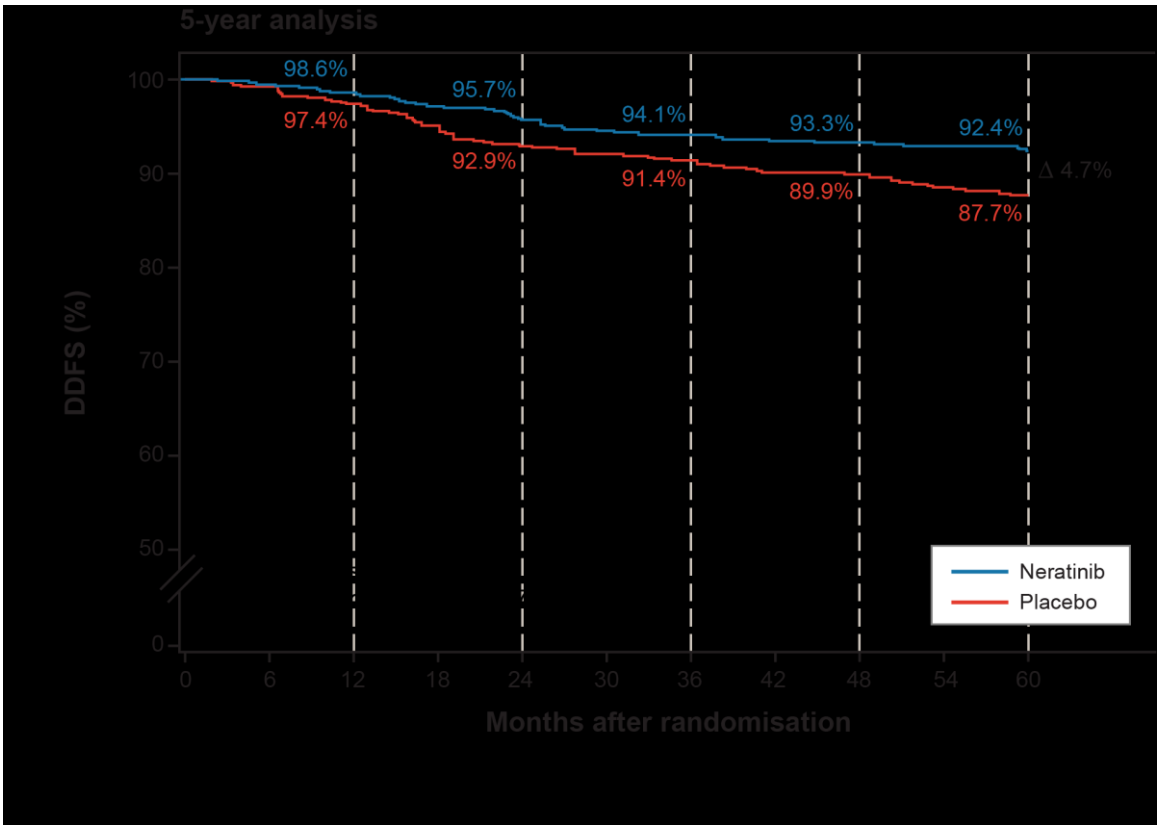
Abbreviations: CI, confidence interval; DDFS, distant disease-free survival; HR+, hormone receptor-positive.

Source: Gnant et al. (2018)[52]

For the ITT population (n = 2,840), there was no significant difference in 2-year DDFS rates, which were 95.3% for neratinib and 94.0% for placebo, with a non-significant relative risk reduction of 26% versus placebo (stratified hazard ratio, 0.74; 95% CI, 0.52-1.05; two-sided *P* = 0.094).[1]

In the label population, the 5-year DDFS rate was 92.4% for neratinib (n = 670) and 87.7% for placebo (n = 664), equating to an absolute benefit of 4.7% and a significant relative risk reduction of 43% versus placebo (42 vs. 75 events; unstratified hazard ratio, 0.57; 95% CI, 0.39-0.83; two-sided *P* = 0.003) (Figure 10).[52]

Figure 10. ExteNET: Kaplan-Meier curve of DDFS at 5 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab



Abbreviations: CI, confidence interval; DDFS, distant disease-free survival; HR+, hormone receptor-positive.

Source: Gnant et al. (2018)[52]

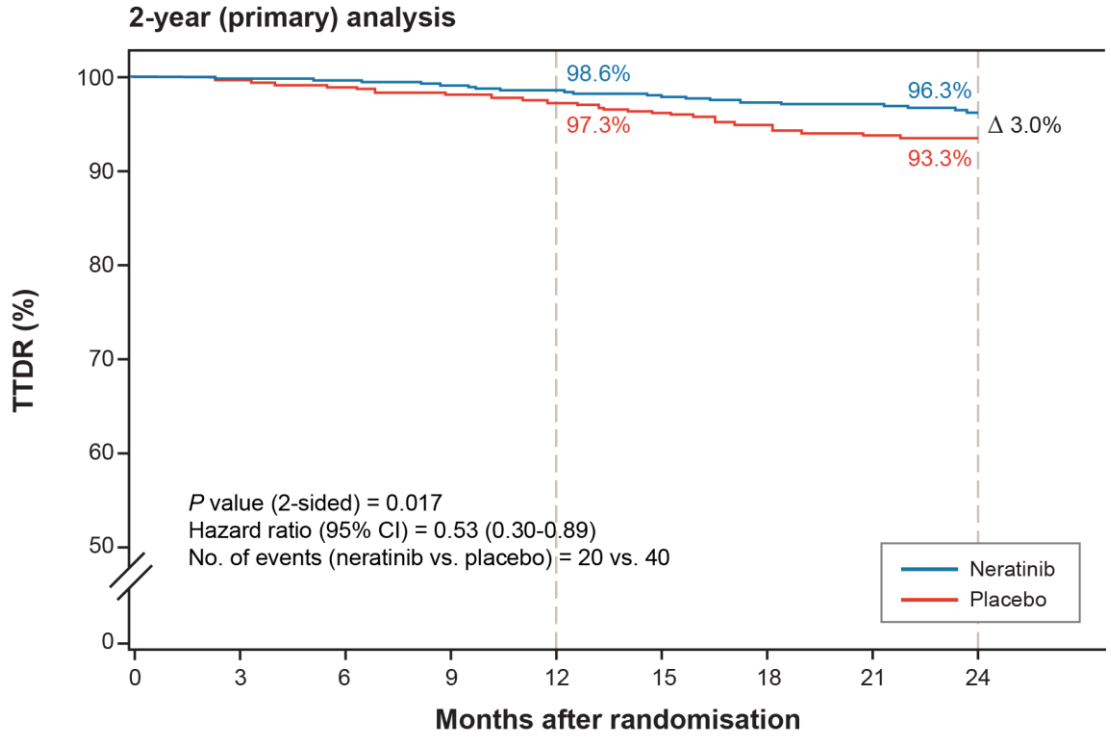
In the ITT population, 5-year DDFS rates were 91.6% for neratinib and 89.9% for placebo, with neratinib reducing the risk of disease recurrence or death by 22% versus placebo (stratified hazard ratio, 0.78; 95% CI, 0.60-1.01; two-sided $P = 0.065$).[47]

Time to distant recurrence

Reflecting the DDFS results, neratinib significantly improved TTDR compared with placebo at 2 years and 5 years after randomisation in the label population but not in the ITT population.

In the label population (n = 1,334), the 2-year TTDR event-free rate was 96.3% for neratinib (n = 670) and 93.3% for placebo (n = 664), equating to an absolute benefit of 3.0% and a relative risk reduction in the time to distant disease recurrence or death of 47% versus placebo (20 vs. 40 events; unstratified hazard ratio, 0.53; 95% CI, 0.30-0.89; two-sided $P = 0.017$) (Figure 11).[1,52] After 5 years, there was a significant relative risk reduction of 42% versus placebo (41 vs. 72 events; unstratified hazard ratio, 0.58; 95% CI, 0.39-0.85; two-sided $P = 0.005$) (Figure 12).[52]

Figure 11. ExteNET: Kaplan-Meier curve of TTDR at 2 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab



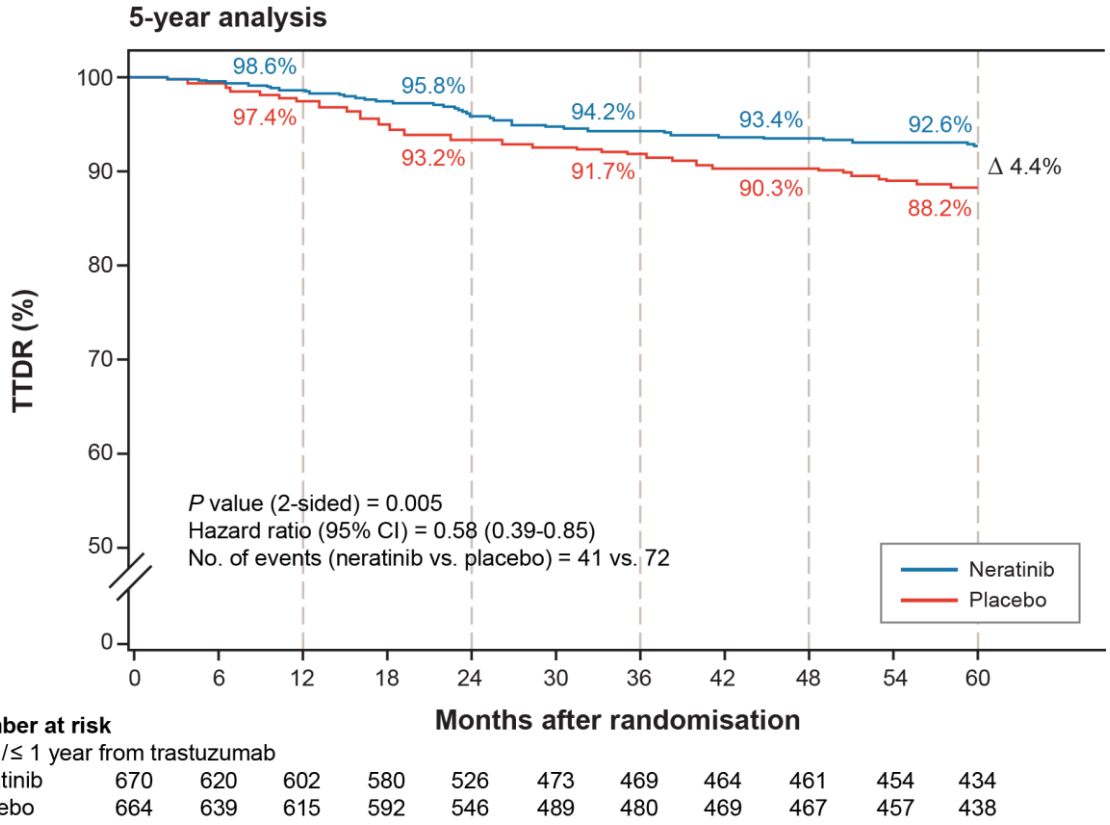
Number at risk

Neratinib	670	606	594	578	561	540	518	488	309
Placebo	664	638	624	609	587	572	551	511	336

Abbreviations: CI, confidence interval; HR+, hormone receptor-positive; TTDR, time to distant recurrence.

Source: Puma data on file (2018)[75]

Figure 12. ExteNET: Kaplan-Meier curve of TTDR at 5 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab



Number at risk
HR+/≤ 1 year from trastuzumab

Neratinib	670	620	602	580	526	473	469	464	461	454	434
Placebo	664	639	615	592	546	489	480	469	467	457	438

Abbreviations: CI, confidence interval; HR+, hormone receptor-positive; TTDR, time to distant recurrence

Source: Puma data on file (2018)[70]

For the ITT population (n = 2,840), there was no significant difference in 2-year TTDR rates, which were 95.5% for neratinib and 94.2% for placebo, with a non-significant relative risk reduction of 27% versus placebo (stratified hazard ratio, 0.73; 95% CI, 0.51-1.04; two-sided *P* = 0.087).[1] After 5 years, TTDR rates were 91.8% for neratinib and 90.3% for placebo, with neratinib improving the time to distant disease recurrence or death by 21% versus placebo (stratified hazard ratio, 0.79; 95% CI, 0.60-1.03; two-sided *P* = 0.078).[47,69]

Rates of central nervous system recurrence

The number of CNS recurrence events was low at both 2 years and 5 years after randomisation in both the label and ITT populations.[52]

In the label population (n = 1,334), the 2-year CNS recurrence incidence rate was 0.34% for neratinib (n = 670) and 1.01% for placebo (n = 664), equating to a non-significant absolute difference of 0.67% (6 vs. 2 events; two-sided *P* = 0.187).[1,52] For the ITT population (n = 2,840), stratified 2-year CNS recurrence rates were 0.92% for neratinib and 1.16% for placebo (0.24% treatment difference; two-sided *P* = 0.548).[1]

In the label population, the 5-year CNS recurrence rate was 0.69% for neratinib and 2.09% for placebo (4 vs. 12 events; *P* = 0.055).[52] In the ITT population, 5-year CNS recurrence rates were 1.30% for neratinib and 1.82% for placebo (0.52% treatment difference; *P* = 0.333).[47]

Overall survival

Overall survival data are not yet mature. This is an event-driven endpoint only powered for the ITT population, and the sponsor/Puma remains blinded until the primary endpoint is reached. The final analysis of the ITT population will be conducted when 248 events have been reported. At the time of the ITT 5-year analysis, 121 deaths had been reported across both treatment groups combined (the OS data remained blinded because the data had not reached maturity; therefore, data by treatment arm were not available) owing to disease progression (n = 102) or other reasons (n = 19).[47] Mature OS data from ExteNET in the HR+ subset is not expected during the appraisal period. While data for the ITT population will read out by [redacted], data for the HR+ subset are expected to be available from [redacted], and the sponsor/Puma remains blinded until then. Blinded OS data for the label population from the latest data cutoff are shown in Figure 13 and were used to validate predictions in the cost-effectiveness model.

Figure 13. ExteNET: Kaplan-Meier curve of blinded OS, HR+ population ≤ 1 year from prior adjuvant trastuzumab

Abbreviations: HR+, hormone receptor-positive; NE, not estimable; OS, overall survival.

Source: Puma data on file (2018)[76]

B.2.6.1.4 ExteNET: Exploratory HRQoL endpoints

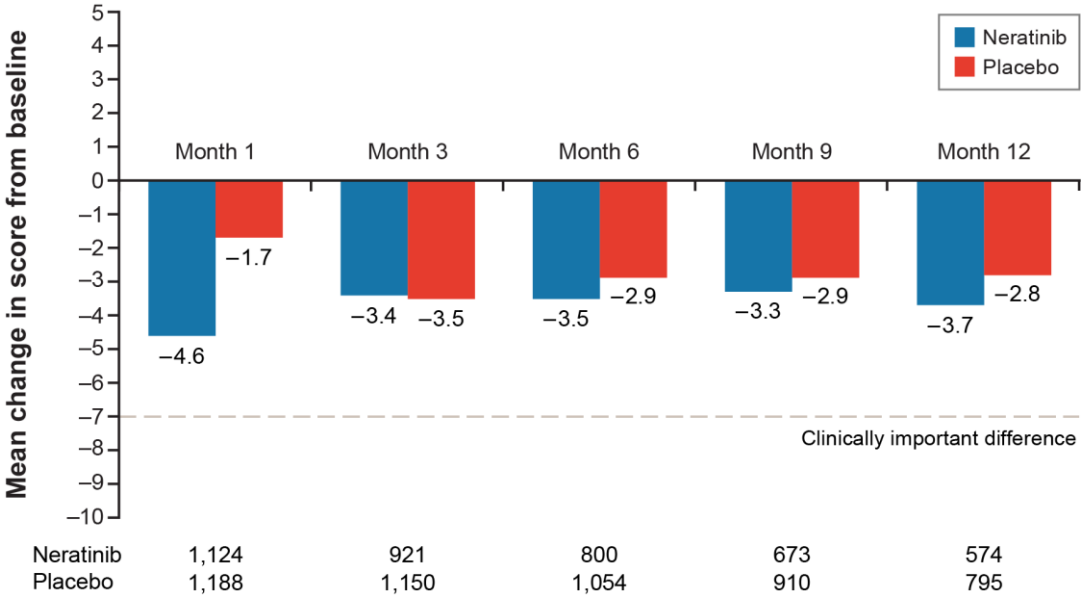
Patient-reported outcomes were measured as exploratory endpoints in ExteNET using the Functional Assessment of Cancer Therapy–Breast (FACT-B) (version 4) and EQ-5D-3L at baseline and months 1, 3, 6, 9, and 12 (end of treatment).[51,53,54] In ExteNET, HRQoL data were collected from 2,407 evaluable ITT participants who completed FACT-B questionnaires at baseline and at least one postbaseline visit (neratinib, n = 1,171; placebo, n = 1,236), and from 2,427 evaluable ITT patients who completed EQ-5D-3L questionnaires at baseline and at least one postbaseline visit (neratinib, n = 1,186; placebo, n = 1,241). In ExteNET, questionnaire completion rates were ≥ 85% from baseline to month 6 in both the neratinib and placebo groups; rates at later time points were lower in both groups (range, 69%-79%) because of a protocol amendment (October 2011) that removed the requirement for HRQoL data collection.[51,54]

HRQoL differences between neratinib and placebo, as measured by the FACT-B and EQ-5D-3L, were greatest after 1 month of treatment in favour of placebo, but these differences did not cross clinically meaningful thresholds (7-8 points for FACT-B total score or previously reported important differences for EQ-5D Index [0.09-0.10 units] or EQ-5D-3L health state [7-10 units])[51,53,54]:

- FACT-B total score: −2.9 points (95% CI, −3.7 to −2.0; $P < 0.0001$)
- EQ-5D-3L Index: −0.02 units (95% CI, −0.03 to −0.01; $P = 0.004$)
- EQ-5D-3L health state: −2.7 units (95% CI, −3.7 to −2.0; $P < 0.0001$)

The decreases in HRQoL observed in the neratinib treatment group after the first month were followed by steady recovery towards baseline over the 12-month study period. Figure 14 and Figure 15 present mean changes from baseline in FACT-B total scores and EQ-5D-3L health-state summary score in ExteNET.[51] The patterns of changes for the EQ-5D-3L Index and health-state scores were similar to those observed with FACT-B (Figure 16, Figure 17, Figure 18).[53] The decrease in the FACT-B and EQ-5D-3L scores in the neratinib group after month 1 may be attributable to the occurrence of treatment-emergent diarrhoea during month 1 (see Section B.2.10.2.1). After month 1, the differences between groups in FACT-B scores were minimal ($P > 0.05$). With the exception of the FACT-B Physical Well-Being subscale score at month 1 (mean difference between groups, −2.4 points), which was of borderline clinical significance, all other between-group differences were less than the previously reported important difference (i.e., less than the lowest estimate for an important difference reported in the literature).[53]

Figure 14. ExteNET: mean changes from baseline in FACT-B total scores by visit

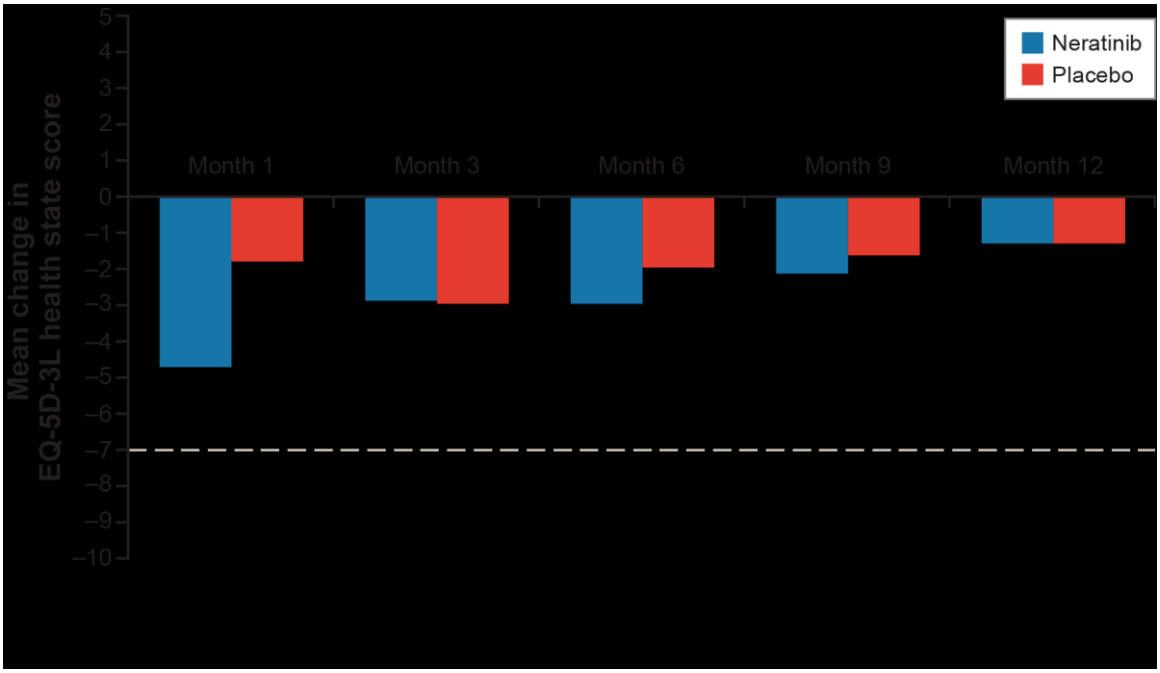


Abbreviation: FACT-B, Functional Assessment of Cancer Therapy–Breast.

Note: A negative change indicates decreased health-related quality of life. The baseline FACT-B score for both neratinib and placebo was 114.4.

Sources: Delaloge et al. (2018)[51]; Puma data on file (2018)[77]

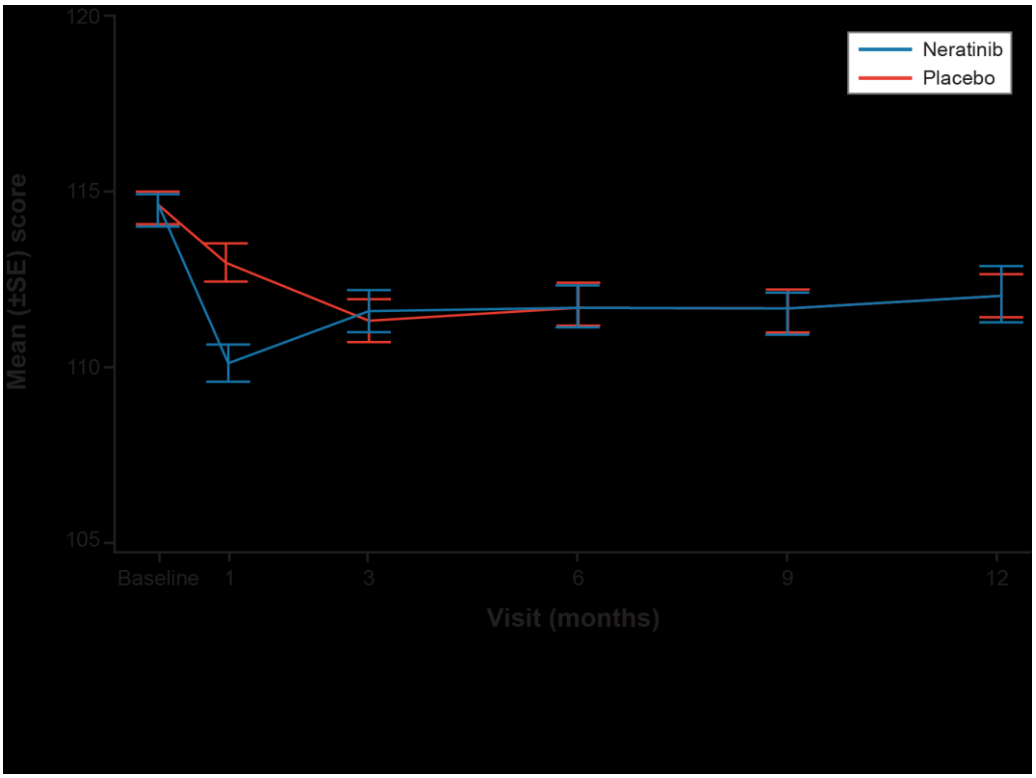
Figure 15. ExteNET: mean changes from baseline in EQ-5D-3L health-state summary scores by visit



Note: A negative change indicates decreased health-related quality of life. Baseline EQ-5D-3L health-state scores were 81.5 for neratinib and 81.6 for placebo.

Source: Puma data on file (2018)[77]

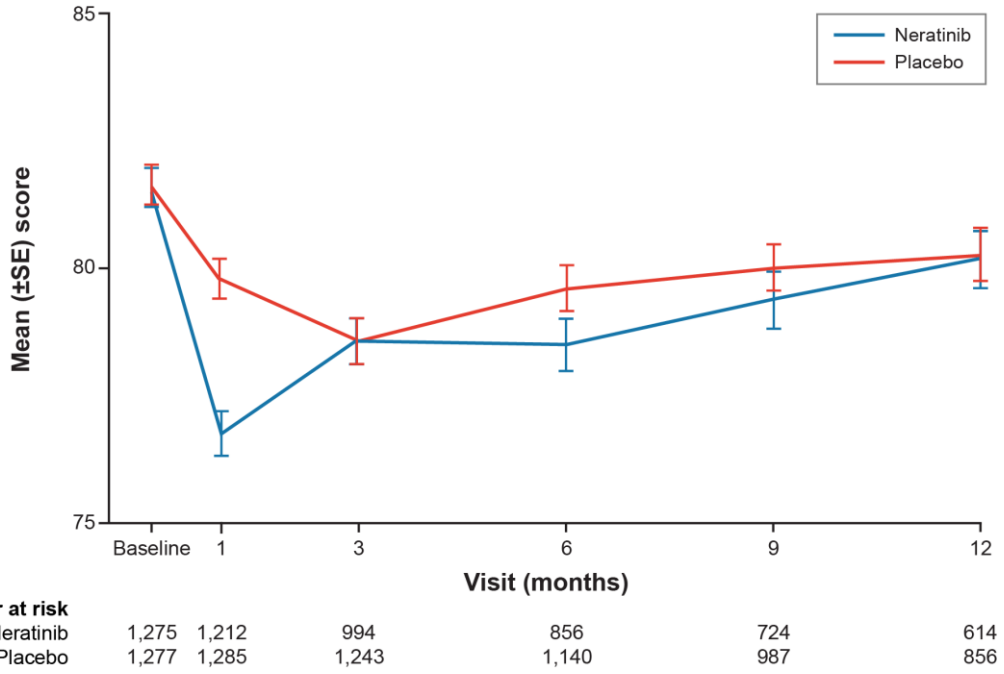
Figure 16. ExteNET: mean FACT-B total scores from baseline to 12 months by treatment group



Abbreviations: FACT-B, Functional Assessment of Cancer Therapy–Breast; SE, standard error.

Source: Delaloge et al. (2017)[53]

Figure 17. ExteNET: mean EQ-5D-3L health-state scores from baseline to 12 months by treatment group

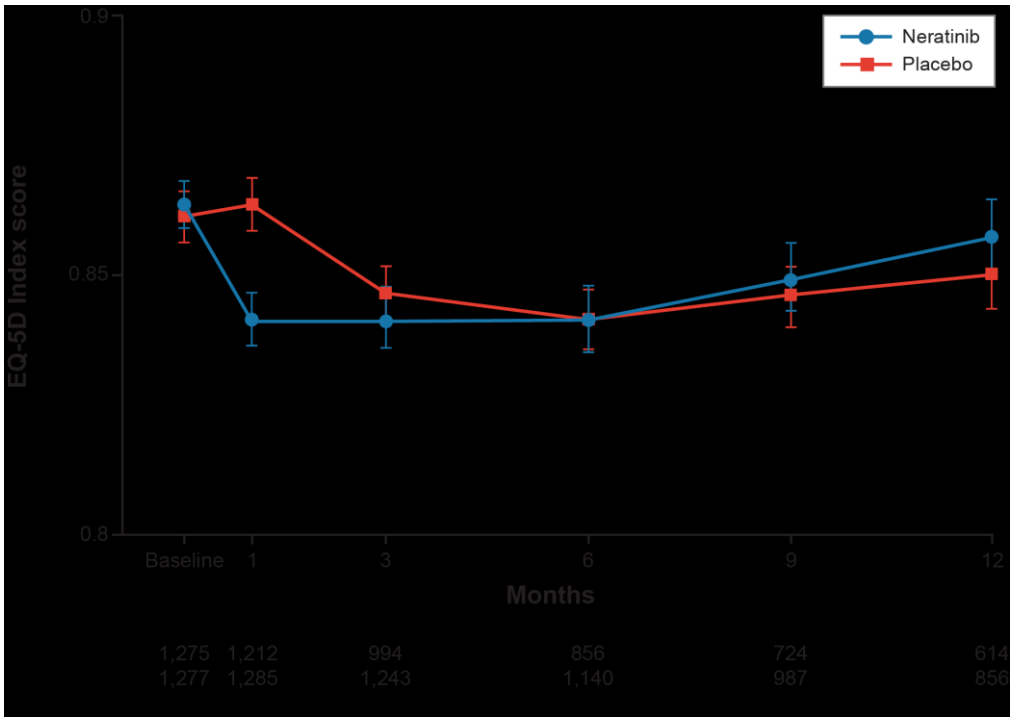


Number at risk						
Neratinib	1,275	1,212	994	856	724	614
Placebo	1,277	1,285	1,243	1,140	987	856

Abbreviation: SE, standard error.

Source: Delaloge et al. (2017)[53]

Figure 18. ExteNET: mean EQ-5D-3L Index from baseline to 12 months by treatment group



Abbreviation: SE, standard error.

Source: Delaloge et al. (2017)[53]

B.2.6.2 CONTROL

The primary outcome of the CONTROL safety trial was incidence of grade 3 diarrhoea at any time during the study. As CONTROL did not include efficacy assessments and instead focused on safety outcomes, the primary results of the CONTROL study are presented in Section B.2.10.3, and only exploratory HRQoL outcomes are presented here.[51,78,79]

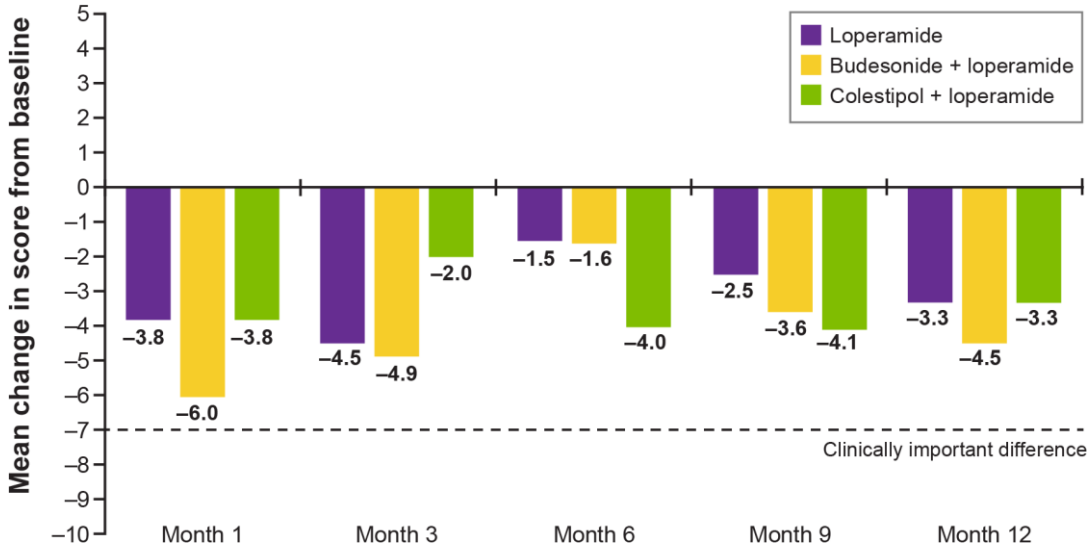
Exploratory HRQoL results presented here are from an interim HRQoL analysis of CONTROL using a cutoff date of October 2018 when all patients in the loperamide and budesonide cohorts had completed therapy with neratinib. Results are for the entire HRQoL population of CONTROL (defined as patients who had received ≥ 1 dose of study treatment, and had a baseline HRQoL assessment and ≥ 1 postbaseline HRQoL assessment), regardless of HR status or time to trastuzumab therapy. In CONTROL, 228 patients were included in the HRQoL population (loperamide, n = 40; budesonide + loperamide, n = 62; colestipol + loperamide, n = 126).[51]

B.2.6.2.1 CONTROL: exploratory HRQoL endpoints

FACT-B

Patients in all three CONTROL cohorts experienced an early transient decrease from baseline in FACT-B total scores (Figure 19). Scores subsequently returned towards baseline over the remainder of the 12-month study, as observed in neratinib-treated patients in ExteNET (Figure 20).[51] Mean changes in FACT-B total scores ranged from −6.0 to −1.5 points over the course of study treatment. In the cohorts that had completed follow-up (neratinib + loperamide and budesonide + loperamide), the largest decreases in FACT-B total scores occurred during months 1 and 3 followed by lower decreases. None of these changes reached the clinically meaningful threshold of 7 to 8 points.[51]

Figure 19. CONTROL: mean changes from baseline in FACT-B total scores by visit



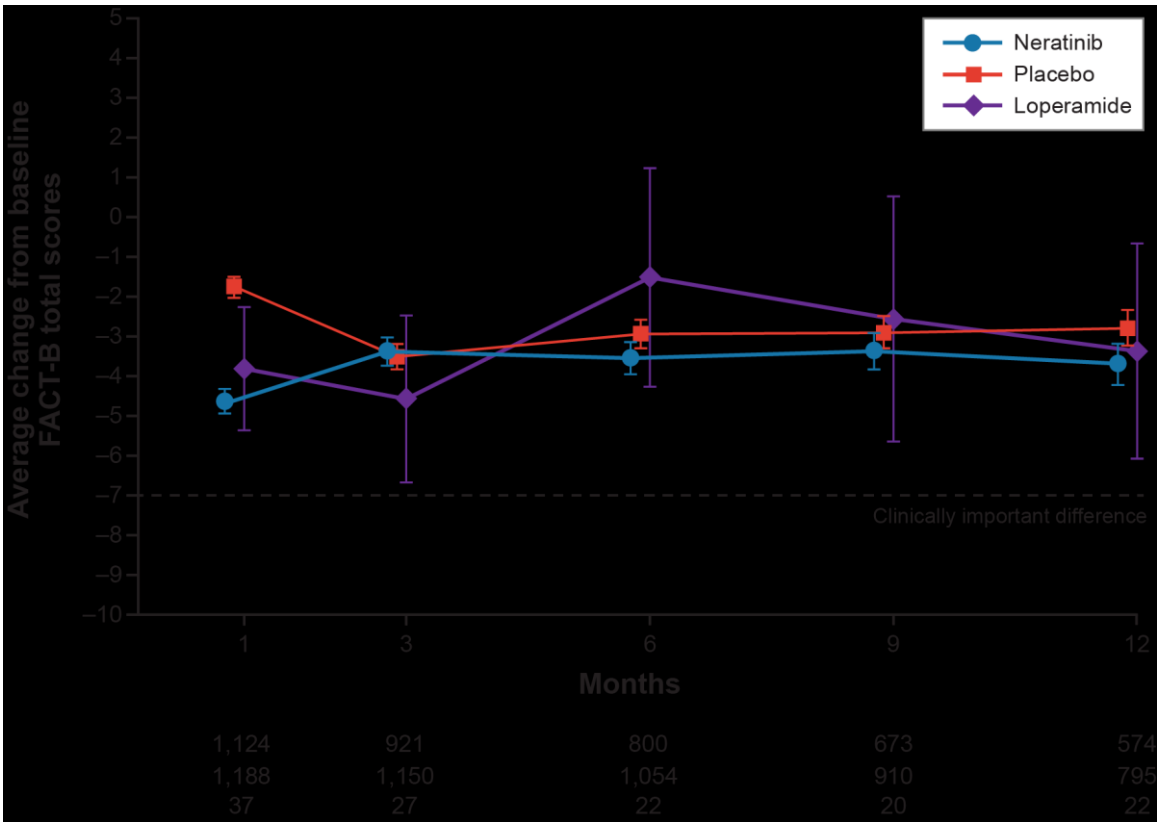
Number of patients	Month 1	Month 3	Month 6	Month 9	Month 12
Loperamide	37	27	22	20	22
Budesonide + loperamide	59	56	51	50	49
Colestipol + loperamide	122	108	102	99	90

Abbreviation: Functional Assessment of Cancer Therapy–Breast.

Note: A negative change indicates decreased health-related quality of life.

Source: Delaloge et al. (2018)[51]

Figure 20. CONTROL: mean change from baseline in FACT-B total scores in ExteNET and CONTROL loperamide cohort



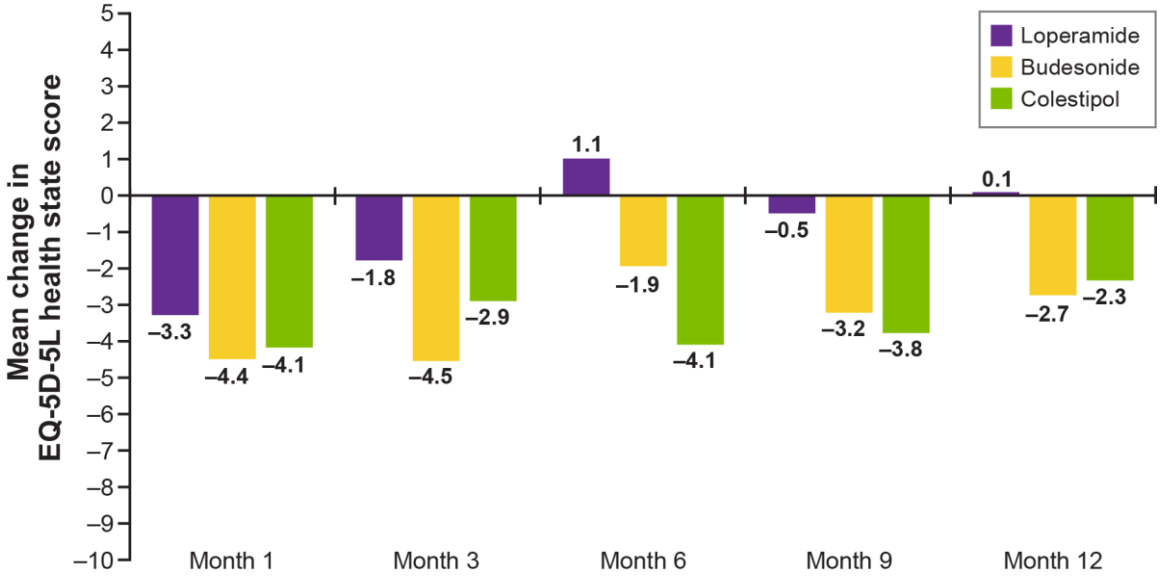
Abbreviation: Functional Assessment of Cancer Therapy–Breast.

Source: Hurvitz et al. (2017)[50]

EQ-5D

In CONTROL, the patterns of changes for the EQ-5D-5L health-state scores (Figure 21) and EQ-5D Index (Figure 22) were similar to those observed with FACT-B. Between-group differences were less than the previously reported important difference (i.e., less than the lowest estimate for an important difference reported in the literature).[78,79]

Figure 21. CONTROL: mean changes from baseline in EQ-5D-5L health-state scores by visit

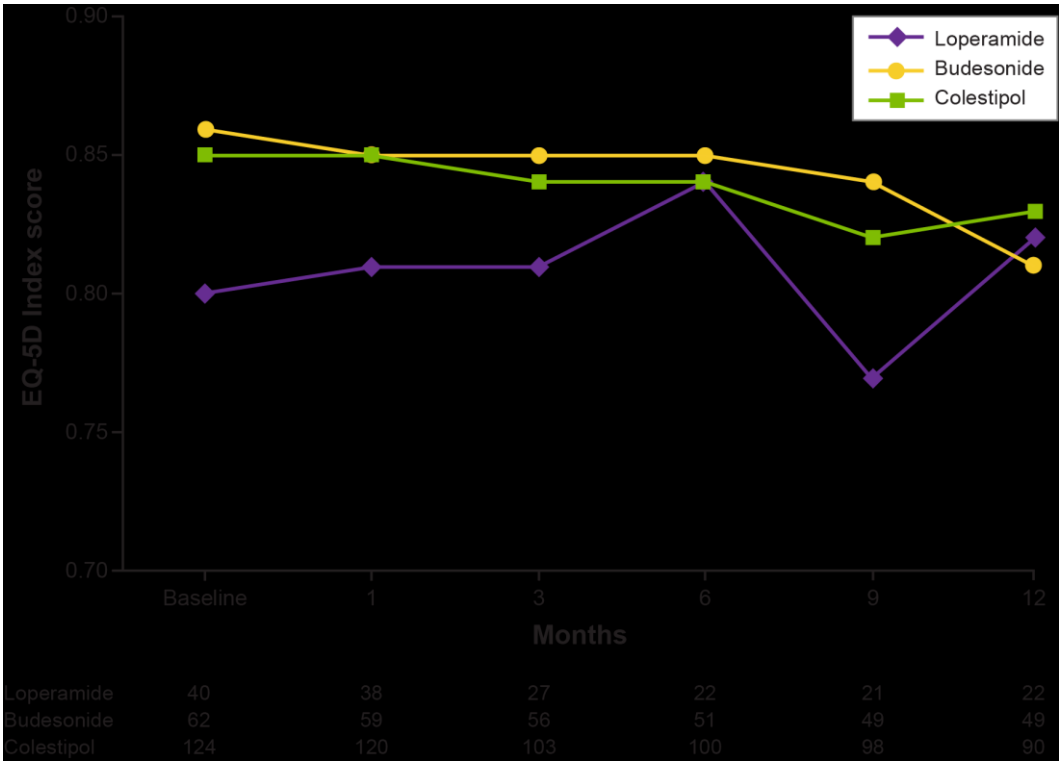


Number of patients					
Loperamide	36	25	20	19	22
Budesonide	59	56	51	50	49
Colestipol	122	108	102	99	90

Note: A negative change indicates decreased health-related quality of life.

Source: Puma data on file (2018)[78]

Figure 22. CONTROL: mean EQ-5D-5L Index from baseline to month 12 by treatment group



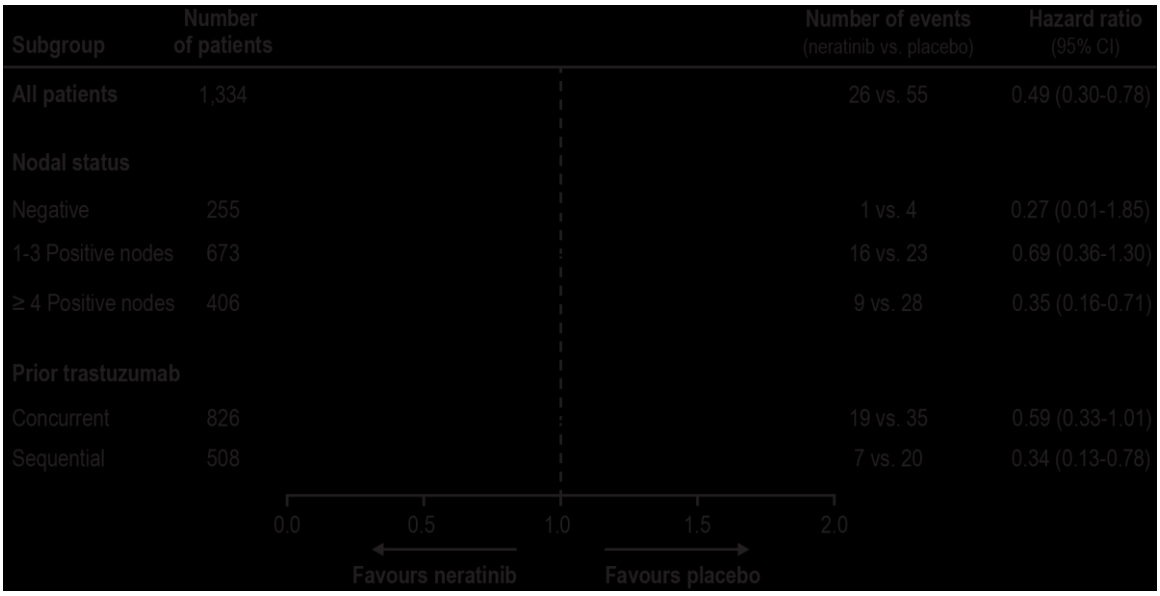
Source: Puma data on file (2018)[79]

B.2.7 Subgroup analysis: ExteNET

B.2.7.1.1 Efficacy results by subgroups in ExteNET

Preplanned subgroup analyses for the ITT population, such as nodal status and concurrent/sequential trastuzumab regimen, were carried out as additional analyses for the label population (HR+ within 1 year of trastuzumab). Figure 23 presents the post hoc analysis of 2-year iDFS for the label population (n = 1,334) for the prespecified subgroups.[1]

Figure 23. ExteNET: 2-year iDFS by subgroup for the label population (n = 1,334)

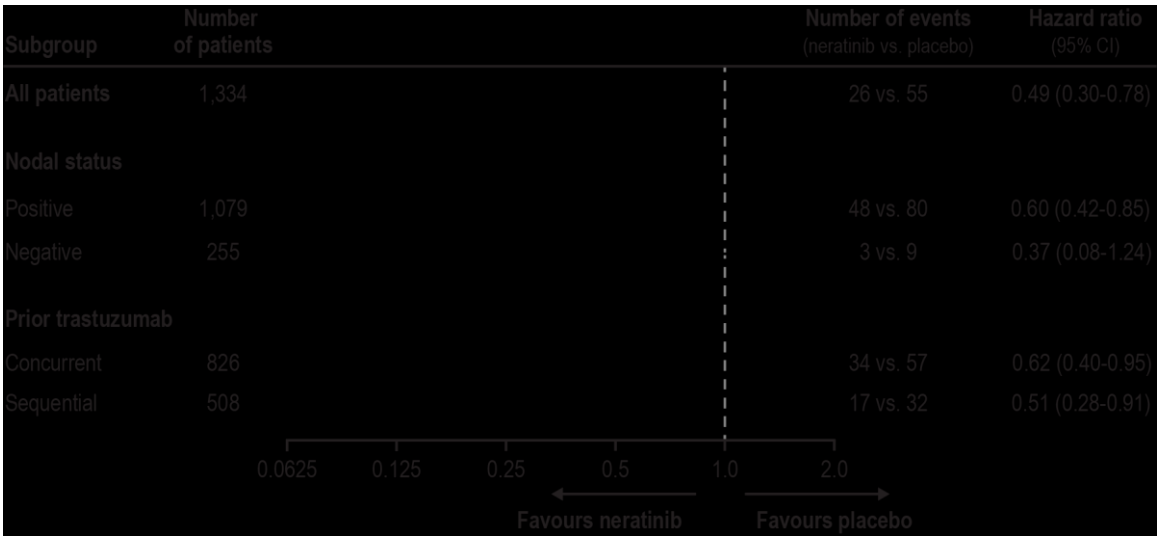


Abbreviations: CI, confidence interval; iDFS, invasive disease-free survival.

Source: NERLYNX® SmPC (2018)[1]

Figure 24 presents the post hoc analysis of 5-year iDFS for the label population (n = 1,334) for the prespecified subgroups.[52]

Figure 24. ExteNET: 5-year iDFS by subgroup for the label population (n = 1,334)



Abbreviation: CI, confidence interval; iDFS, invasive disease-free survival.
Source: Gnant et al. (2018)[52]

B.2.8 Meta-analysis

A meta-analysis requires two or more studies that contain the intervention of interest. Therefore, a meta-analysis for the primary efficacy outcome of iDFS was not possible, as only one randomised study (ExteNET) has reported iDFS for neratinib.

B.2.9 Indirect and mixed-treatment comparisons

There are no approved treatments in the extended adjuvant setting after 1 year of treatment with trastuzumab, and there is no appropriate comparator to perform an indirect or mixed-treatment comparison with neratinib.

B.2.10 Adverse reactions

Neratinib, with prophylaxis for diarrhoea, has a predictable and manageable safety profile.[47] The most common adverse reaction associated with neratinib is diarrhoea, which can be managed by using a structured loperamide prophylaxis regimen in the first cycle of treatment.[50]

Two studies were identified that reported adverse reactions and other safety outcomes with neratinib in early HR+/HER2+ breast cancer: ExteNET and CONTROL. The safety population of CONTROL (n = 321) included all patients with HER2+ breast cancer, regardless of HR status or time from completion of trastuzumab therapy, which was compared with the neratinib groups from the ExteNET safety population (n = 1,420) as a historical comparator.[50]

B.2.10.1 ExteNET: overall safety summary

In ExteNET, at least one dose of study treatment was received by 2,816 patients (n = 1,408 patients in each group) representing the safety population. Results presented here are the primary 2-year analyses for the entire safety population for ExteNET, regardless of HR status or time from completion of trastuzumab therapy (n = 2,816)[48] and a subgroup analysis for the label population relevant to the NICE decision problem (n = 1,319: neratinib, n = 662; placebo, n = 657).[52,80] Median duration of treatment was similar between treatment arms in the label population: 11.5 months in the neratinib group and 11.9 months in the placebo group.[52]

The profile and frequency of adverse events in the safety population and the label population were similar (Table 19 and Table 20).[48,52] The most frequently reported treatment-emergent adverse events (TEAEs) with neratinib in both the safety and label population were gastrointestinal (GI) disorders, including diarrhoea, nausea, vomiting, and abdominal pain (Table 21 and Table 22). Other frequently reported TEAEs included fatigue, headache, rash, decreased appetite, muscle spasms, and dizziness (Table 21 and Table 22).[48,52]

In the safety population, TEAEs causing discontinuation of the study drug occurred in 388 (28.0%) patients with neratinib and 76 (5.0%) with placebo.[47] Serious TEAEs occurred in 103 (7%) patients in the neratinib group and 85 (6%) in the placebo group (Table 19). The most common serious events in the neratinib group were diarrhoea, vomiting, and dehydration. Reported deaths were due to metastatic breast cancer, including metastases that had infiltrated the meninges (n = 1), and acute myeloid leukaemia (n = 1) in the neratinib group and gastric cancer (n = 1) in the placebo group. None of these deaths were attributed to study treatment in either group.[47]

For the label population, the profile and frequency of TEAEs leading to dose reductions, dose holds, and hospitalisation were similar to the safety population in 203 (31%), 280 (42%), and 41 (6%) patients in the neratinib group, respectively, and 13 (2%), 75 (11%), and 35 (5%) patients in the placebo group (Table 20).[52]

Table 19. ExteNET: overall summary of TEAEs, safety population

TEAE	Neratinib (n = 1,408), n (%)	Placebo (n = 1,408), n (%)	Total (N = 2,816), n (%)
Any TEAE	1,387 (98.5)	1,240 (88.1)	2,627 (93.3)
Grade 3 or 4 TEAE	700 (49.7)	184 (13.1)	884 (31.4)
Fatal TEAE	2 (0.1)	1 (0.1)	3 (0.1)
Serious TEAE (SAE)	103 (7.3)	85 (6.0)	188 (6.7)
Treatment-related TEAE	1,353 (96.1)	805 (57.2)	2,158 (76.6)

TEAE	Neratinib (n = 1,408), n (%)	Placebo (n = 1,408), n (%)	Total (N = 2,816), n (%)
Serious treatment-related TEAE	42 (3.0)	8 (0.6)	50 (1.8)
TEAE leading to treatment discontinuation	388 (27.6)	76 (5.4)	464 (16.5)
TEAE leading to study withdrawal	32 (2.3)	7 (0.5)	39 (1.4)
TEAE leading to dose reduction	440 (31.3)	35 (2.5)	475 (16.9)
TEAE leading to hospitalisation	93 (6.6)	75 (5.3)	168 (6.0)
TEAE leading to dose hold	629 (44.7)	187 (13.3)	816 (29.0)

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: Puma data on file (2016)[61]

Table 20. ExteNET: overall summary of TEAEs for HR+ patients who completed prior adjuvant trastuzumab within 1 year from randomisation, label safety population

TEAE	Neratinib (n = 662), n (%)	Placebo (n = 657), n (%)	Total (N = 1,319), n (%)
Any TEAE	649 (98.0)	567 (86.3)	1,216 (92.2)
Grade 3 or 4 TEAE	327 (49.4)	76 (11.6)	403 (30.6)
Fatal TEAE	1 (0.2)	0 (0.0)	1 (0.1)
Serious TEAE (SAE)	45 (6.8)	36 (5.5)	81 (6.1)
Treatment-related TEAE	630 (95.2)	360 (54.8)	990 (75.1)
Serious Treatment-related TEAE	19 (2.9)	5 (0.8)	24 (1.8)
TEAE leading to treatment discontinuation	178 (26.9)	30 (4.6)	208 (15.8)
TEAE leading to study withdrawal	11 (1.7)	2 (0.3)	13 (1.0)
TEAE leading to dose reduction	203 (30.7)	13 (2.0)	216 (16.4)
TEAE leading to hospitalisation	41 (6.2)	35 (5.3)	76 (5.8)
TEAE leading to dose hold	280 (42.3)	75 (11.4)	355 (26.9)

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: Puma data on file (2018)[80]

Table 21. ExteNET: grade 1-4 TEAEs occurring in ≥ 10%, safety population

	Neratinib (n = 1,408)			Placebo (n = 1,408)		
Adverse event	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Diarrhoea	781 (55)	561 (40)	1 (< 1)	476 (34)	23 (2)	0
Nausea	579 (41)	26 (2)	0	301 (21)	2 (< 1)	0
Fatigue	359 (25)	23 (2)	0	276 (20)	6 (< 1)	0
Vomiting	322 (23)	47 (3)	0	107 (8)	5 (< 1)	0
Abdominal pain	314 (22)	24 (2)	0	141 (10)	3 (< 1)	0
Upper abdominal pain	201 (14)	11 (1)	0	93 (7)	3 (< 1)	0
Rash	205 (15)	5 (< 1)	0	100 (7)	0	0
Decreased appetite	166 (12)	3 (< 1)	0	40 (3)	0	0
Muscle spasms	157 (11)	1 (< 1)	0	44 (3)	1 (< 1)	0

Adverse event	Neratinib (n = 1,408)			Placebo (n = 1,408)		
	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Dizziness	143 (10)	3 (< 1)	0	125 (9)	3 (< 1)	0
Arthralgia	84 (6)	2 (< 1)	0	158 (11)	4 (< 1)	0

Abbreviation: TEAE, treatment-emergent adverse event.

Source: Martin et al. (2017)[47]

Table 22. ExteNET: grade 1-4 TEAEs occurring in ≥ 10%, label safety population

Adverse event	Neratinib (n = 662)			Placebo (n = 657)		
	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Diarrhoea	365 (55.1)	261 (39.4)	0	213 (32.4)	7 (1.1)	0
Nausea	280 (42.3)	9 (1.4)	0	135 (20.5)	2 (0.3)	0
Fatigue	177 (26.7)	13 (2.0)	0	129 (19.6)	2 (0.3)	0
Vomiting	150 (22.7)	24 (3.6)	0	41 (6.2)	2 (0.3)	0
Abdominal pain	145 (21.9)	11 (1.7)	0	58 (8.8)	1 (0.2)	0
Headache	119 (18.0)	6 (0.9)	0	125 (19.0)	1 (0.2)	0
Upper abdominal pain	90 (13.6)	6 (0.9)	0	35 (5.3)	3 (0.5)	0
Rash	90 (13.6)	3 (0.5)	0	40 (6.1)	0	0
Decreased appetite	79 (11.9)	1 (0.2)	0	13 (2.0)	0	0
Muscle spasms	81 (12.2)	0	0	21 (3.2)	1 (0.2)	0

Abbreviation: TEAE, treatment-emergent adverse event.

Source: Puma data on file (2019)[81]

B.2.10.2 ExteNET: incidence of diarrhoea

Diarrhoea was the most common TEAE with neratinib treatment in ExteNET, in both the entire safety population (95.4% with neratinib vs. 35.4% with placebo)[82] and the label safety population (93.7% with neratinib vs. 28.2% with placebo).[83] Diarrhoea is an expected on-target side effect of an EGFR-targeted agent, likely attributable to EGFR involvement in calcium-dependent chloride transport because EGFR inhibition (the postulated mechanism of neratinib's effect) might result in secretory diarrhoea.[47] In ExteNET, no mandatory treatment with antidiarrhoeal prophylaxis was specified in the protocol.

In the safety population, 55% in neratinib group versus 34% in placebo group had grade 1-2 diarrhoea; 40% in neratinib group versus 2% in placebo group had grade 3 diarrhoea; and 1 patient (< 1%) in neratinib group versus none (0%) in placebo group had grade 4 diarrhoea (Table 23).[48] Results were similar in the label population, but no patients in either group experienced grade 4 diarrhoea (Table 23).[83]

Severe (grade 3) diarrhoea associated with neratinib in ExteNET occurred early (in the first month of treatment) and was mostly self-limiting (Table 23). In the safety population, grade 3 diarrhoea occurred after a median of 8 days (IQR, 4-33 days) and lasted a median of 5 days (IQR, 2-9 days) per patient. Most grade 3 diarrhoea events occurred in the first month of treatment. Diarrhoea led to neratinib dose reductions in 372 (26%) patients in the neratinib group and 8 (1%) in the placebo group, hospital admission in 20 (1%) patients versus 1 (< 1%), and drug discontinuation in 237 (17%) patients (discontinued after a median of 20 days [IQR, 9-56 days]) versus 3 (< 1%) (discontinued after 241 days [IQR, 147-305 days]), respectively.[48] The incidence of grade 3 diarrhoea in the label population was similar (Table 23).[83]

Apart from GI events, all other grade 3-4 AEs occurred in fewer than 4% of neratinib-treated patients, with a similar incidence of non-GI events in both groups. There was no evidence suggesting a cumulative increase in long-term or irreversible toxicities, specifically symptomatic cardiac toxicity or second primary malignancies in the neratinib group compared with the placebo group.[47]

Table 23. ExteNET: treatment-emergent diarrhoea, safety population

Event no. (%) unless otherwise specified	Neratinib (n = 1,408)	Placebo (n = 1,408)
Patients ever experienced treatment-emergent diarrhoea, no. (%)	1,343 (95.4)	499 (35.4)
Maximum toxicity, no. (%)		
Grade 1	323 (22.9)	382 (27.1)
Grade 2	458 (32.5)	94 (6.7)
Grade 3	561 (39.8)	23 (1.6)
Grade 4	1 (0.1)	0
Drug-related diarrhoea, no. (%)	1,330 (94.5)	411 (29.2)
Serious events, no. (%)	22 (1.6)	1 (0.1)
Actions taken because of diarrhoea, no. (%)		
Withdrawn from study	23 (1.6)	0
Discontinued study drug	237 (16.8)	3 (0.2)
Dose reduction	372 (26.4)	8 (0.6)
Hospitalised	20 (1.4)	1 (0.1)
Dose hold, no. (%)		
Once	263 (18.7)	22 (1.6)
Twice	97 (6.9)	2 (0.1)
Three or more times	117 (8.3)	2 (0.1)
Median (IQR) time to onset of diarrhoea, days		
Any grade	2 (2-4)	18 (4-82)
Grade ≥ 2	5 (2-15)	90 (17-189)

Event no. (%) unless otherwise specified	Neratinib (n = 1,408)	Placebo (n = 1,408)
Grade ≥ 3	8 (4-33)	124 (21-257)
Duration of grade ≥ 3 diarrhoea per patient, days		
Median (IQR)	5 (2-9)	2 (1-5)
Grade ≥ 3 events per patient, no.		
Mean	2.7	1.3
Median (IQR)	2 (1-3)	1 (1-1)
Median (IQR) duration of diarrhoea per event, days		
Any grade	2 (1-3)	2 (1-3)
Grade ≥ 2	1 (1-2)	2 (1-2)
Grade ≥ 3	2 (1-3)	2 (1-4)

Abbreviation: IQR, interquartile range.

Source: Chan et al. (2016)[48]

Table 24. ExteNET: treatment-emergent diarrhoea by treatment month for patients who completed prior adjuvant trastuzumab within 1 year from randomisation and HR+, label safety population

Events, no. (%) unless otherwise specified	Neratinib (n = 662)	Placebo (n = 657)
Patients ever experienced diarrhoea, no. (%)	626 (94.6)	220 (33.5)
Serious events	8 (1.2)	0 (0.0)
Treatment-related	620 (93.7)	185 (28.2)
Serious treatment-related events	8 (1.2)	0 (0.0)
Action taken because of diarrhoea		
IP discontinuation	107 (16.2)	1 (0.2)
Withdrawal from study	10 (1.5)	0 (0.0)
IP reduction	169 (25.5)	4 (0.6)
Temporarily stopping IP	209 (31.6)	9 (1.4)
Hospitalisation	8 (1.2)	0 (0.0)
Concomitant medication	565 (85.3)	94 (14.3)
Other	68 (10.3)	3 (0.5)
Maximum toxicity, n (%)		
Grade 1	153 (23.1)	169 (25.7)
Grade 2	212 (32.0)	44 (6.7)
Grade 3	261 (39.4)	7 (1.1)
Grade 4	0 (0.0)	0 (0.0)
Outcome of the last diarrhoea episode, n (%)		
Persisted	38 (5.7)	7 (1.1)
Resolved	588 (88.8)	213 (32.4)
Time to first onset in days (any grade)		
Mean (SD)	5.95 (20.32)	55.30 (85.36)
Median (IQR)	2.00 (2.00-4.00)	12.50 (4.00-68.50)

Events, no. (%) unless otherwise specified	Neratinib (n = 662)	Placebo (n = 657)
Time to first onset in days (grade ≥ 3)		
Mean (SD)	38.79 (67.15)	215.86 (124.08)
Median (IQR)	8.00 (3.00-32.00)	240.00 (102.00-325.00)
Cumulative duration per patient in days (any grade)		
Mean (SD)	102.36 (116.69)	39.51 (82.12)
Median (IQR)	52.00 (13.00-160.00)	7.00 (2.00-33.50)
Cumulative duration per patient in days (grade ≥ 3)		
Mean (SD)	8.22 (12.54)	5.14 (8.30)
Median (IQR)	5.00 (2.00-9.00)	1.00 (1.00-8.00)
Duration per episode in days (any grade)		
Mean (SD)	5.94 (26.29)	6.15 (31.17)
Median (IQR)	2.00 (1.00-3.00)	2.00 (1.00-3.00)
Duration per episode in days (grade ≥ 3)		
Mean (SD)	3.02 (6.53)	4.00 (4.50)
Median (IQR)	2.00 (1.00-3.00)	1.00 (1.00-8.00)

Abbreviation: HR, hormone receptor; IP, investigational product; SD, standard deviation.

Notes: Worst grade in the specified time period is presented; one month = 30 days.

Source: Puma data on file (2018)[80]

B.2.10.2.1 ExteNET: effects of diarrhoea on HRQoL

The effects of diarrhoea on HRQoL in the ExteNET study were evaluated using the FACT-B scale.[53,54] The highest mean Physical Well-Being score (24.5) was observed for patients with no or grade 1 diarrhoea, followed by patients with grade 2 diarrhoea (22.9), while patients with grade ≥ 3 diarrhoea had the lowest score (21.8). The difference between patients with grade ≥ 3 diarrhoea and those with no or grade 1 diarrhoea was within the previously reported important difference range (2-3 points). For the remaining scales, any differences by diarrhoea grade were less than the important difference range.

B.2.10.3 CONTROL: overall safety summary

CONTROL is an ongoing phase 2, open-label safety and tolerability study investigating the effect of antidiarrhoeal strategies (such as loperamide prophylaxis with and without budesonide or colestipol) on the incidence and duration of neratinib-associated diarrhoea, when compared with a historical cohort from the safety population of the ExteNET study (no protocol-mandated loperamide prophylaxis).[50] Further details of the CONTROL methodology and baseline characteristics are described in in Sections B.2.3.2.1 and B.2.3.2.3.

Safety results presented here are from an interim analysis of CONTROL using a cutoff date of 3 November 2017 when all patients in the loperamide and budesonide cohorts had completed therapy with neratinib. Results are for the entire safety population of CONTROL (all patients who received ≥ 1 neratinib dose), regardless of HR status or time to trastuzumab therapy.[50]

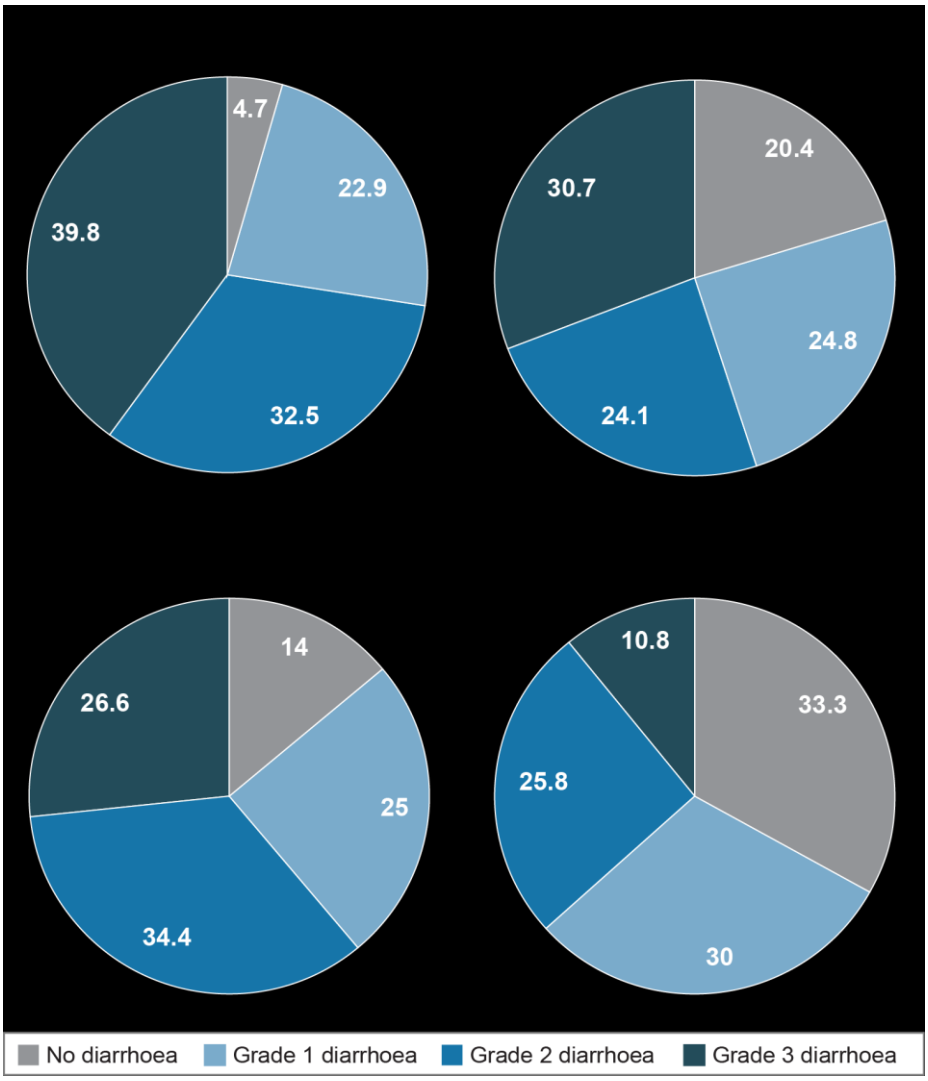
All patients in the loperamide cohorts had completed or prematurely discontinued planned neratinib treatment at the cutoff date; treatment is ongoing in 27% of patients in the budesonide cohort and 79% of patients in the colestipol cohort. At the data cutoff, the median duration of neratinib treatment in the loperamide, budesonide, and colestipol cohorts was 11.5, 11.9, and 3.7 months, respectively. The median neratinib treatment duration in ExteNET was 11.6 (range, 0.1-13.3) months. A final analysis of CONTROL will be reported after all patients have completed the planned 12 months of neratinib therapy in the ongoing cohorts.[50]

B.2.10.4 CONTROL primary outcome: incidence of grade 3 diarrhoea

Interim analyses of CONTROL show structured loperamide prophylaxis in the first cycle of neratinib treatment reduced the incidence, severity, and duration of neratinib-associated diarrhoea compared with ExteNET.[50]

Incidence of grade ≥ 3 diarrhoea at any time during neratinib treatment was 30.7% (95% CI, 23.1%-39.1%) in the loperamide cohort, 26.6% (95% CI, 16.3%-39.1%) in the budesonide cohort, and 10.8% (95% CI, 5.9%-17.8%) in the colestipol cohort compared with 39.9% (95% CI, 37.3%-42.5%) without protocol-mandated loperamide prophylaxis in the ExteNET trial (Figure 25).[50]

Figure 25. Incidence of diarrhoea by grade in CONTROL versus neratinib-treated patients in ExteNET



Source: Hurvitz et al. (2017)[50]

In the CONTROL trial, there were marked reductions in the median cumulative duration of diarrhoea and the median number of diarrhoea episodes per patient with loperamide prophylaxis compared with the ExteNET trial. With loperamide prophylaxis, the median cumulative duration of any grade of diarrhoea was reduced to 14 days (range, 5-63 days) compared with 59 days (range, 14-164 days) without structured prophylaxis in ExteNET.[50] For each of the study cohorts in CONTROL, diarrhoea was characterised by a lower percentage of high-grade diarrhoea (grades 2 and 3) in month 1 and a much lower incidence in months 2 through 12 than was reported in the ExteNET trial. Neratinib dose holds and dose reductions due to diarrhoea were less common in the CONTROL study compared with the ExteNET study. Diarrhoea-related neratinib discontinuation rates decreased in each successive cohort (20% for loperamide, 11% for budesonide, and 2% for colestipol)

and were less frequent with budesonide and colestipol versus ExteNET (17%).[50] Table 25 presents a summary of treatment-emergent diarrhoea characteristics.

Table 25. Characteristics of treatment-emergent diarrhoea in CONTROL compared with ExteNET

	Loperamide (n = 137)	Budesonide + loperamide (n = 64)	Colestipol + loperamide (n = 120)	ExteNET neratinib arm (loperamide as needed) (n = 1,408)
Median cumulative duration, days				
Any grade	14.0	24.0	16.0	59.0
Grade ≥ 2	5.0	6.0	3.5	10.0
Grade ≥ 3[a]	3.0	2.0	3.0	5.0[a]
Median diarrhoea episodes per patient				
Any grade	2	9	2.5	8
Grade ≥ 2	2	3	1	3
Grade ≥ 3[a]	1	1	1	2[a]
Action taken, %				
Dose hold	15.3	18.8	9.2	33.9
Dose reduction	7.3	3.1	4.2	26.4
Discontinuation	20.4	10.9	1.7	16.8
Hospitalisation	1.5	0	0	1.4

[a] One grade 4 event in ExteNET.

Source: Hurvitz et al. (2017)[50]

B.2.10.5 CONTROL: overall adverse events

Aside from diarrhoea, the overall tolerability profile of neratinib with structured antidiarrhoeal prophylaxis (such as loperamide given with or without budesonide or colestipol) was similar to that reported in ExteNET, apart from an increase in grade 1 or 2 constipation. Rates of grade 1/2 constipation in the loperamide, budesonide, and colestipol cohorts were 42.3%/14.6%, 62.5%/12.5%, and 53.3%/9.2%, respectively. No grade 3 or higher constipation has been observed to date. The observed rates of constipation are likely due to the structured loperamide regimens mandated in CONTROL and are not anticipated in clinical practice because the label directs patients to titrate antidiarrhoeal treatment to one or two stools per day.[1]

Table 26 presents the most frequently reported grade 3/4 events. Reported grade 4 events (SAEs) were sepsis and urinary tract infection (both unrelated events in the same patient); there were no fatal AEs reported.[50]

Table 26. CONTROL: most common grade 3 or 4 treatment-emergent adverse events (≥ 1% total incidence) versus neratinib-treated patients in ExteNET

Grade 3 or 4 TEAE, %	Loperamide (n = 137)	Budesonide (n = 64)	Colestipol (n = 120)	ExteNET neratinib arm (n = 1,408)
Diarrhoea	30.7	26.6	10.8	39.9
Fatigue	3.6	7.8	1.7	1.6
Vomiting	1.5	3.1	1.7	3.3
Abdominal pain	1.5	1.6	0.8	1.7
Dehydration	1.5	1.6	0.8	0.9

Abbreviation: TEAE, treatment-emergent adverse event.

Source: Hurvitz et al. (2017)[50]

B.2.11 Ongoing studies

All relevant studies described remain in follow-up, with additional data cuts anticipated over the next few years (Table 27).

Table 27. Additional data anticipated from neratinib trials in the next 12 months

Trial	Next anticipated publication	Analyses anticipated
ExteNET	[redacted]	OS data are not yet mature: the final analysis will be conducted when 248 events have been reported. At the time of the 5-year analysis, 121 deaths had been reported (in both treatment groups combined because OS data remained masked because the data had not yet reached maturity) due to disease progression (n = 102) or other reasons.[47]
CONTROL	[redacted]	Data from CONTROL are not yet mature; although the loperamide cohort have completed the study, treatment in the budesonide and colestipol cohorts is ongoing.[50] In addition, the following three further cohorts are recruiting that will investigate the safety profile using loperamide as needed and initiating neratinib with a dose escalation[55]: • Neratinib + colestipol + loperamide as needed (recruiting) • Neratinib dose escalation in cycle 1 + loperamide as needed (recruiting) • Neratinib dose escalation in cycle 2 + loperamide as needed (recruiting) A final analysis of CONTROL will be reported after all patients have completed the planned 12 months of neratinib therapy in the remaining cohorts.[50,55]

Abbreviation: OS, overall survival.

B.2.12 Innovation

After adjuvant trastuzumab, most women with early HR+/HER2+ breast cancer in the UK do not receive any further treatment, except endocrine therapy.[38] Alternative HER2-targeted adjuvant regimens used after 1 year of trastuzumab-based therapy have shown limited efficacy in further reducing the risk of recurrence in patients with early HER2+ breast cancer. As such, there are no recommended HER2-targeted therapies for early HR+/HER2+ breast cancer in the extended adjuvant setting available routinely in the UK NHS.[41-43]

Neratinib is an orally administered HER2-targeted therapy, obviating the need for administration visits, venous access and port maintenance, without the risk of clotting or infection.[1] Also, oral administration of neratinib is more convenient for the healthcare system and patients and may lead to an improvement in patient compliance.[1]

Patients with HR+ tumours may derive more benefit from neratinib than those with HR– tumours[6] because of its simultaneous blockade of ErbB receptors. This may inhibit the ER/HER2 bidirectional cross talk that promotes the development of drug resistance to both HER2-targeted agents and endocrine therapy, which can contribute to disease recurrence in patients with HR+/HER2+ breast cancer.[5,6] With neratinib, dual blockade of ER and HER2 signalling pathways in HR+/HER2+ breast cancer may result in enhanced an d sustained anti-tumour activity because extended ErbB blockage may re-sensitise the ER signalling pathway to endocrine therapy.[5,6]

B.2.13 Interpretation of clinical effectiveness and safety evidence

- Neratinib is the first therapy that significantly reduces the risk of disease recurrence in patients with early HR+/HER2+ breast cancer in the extended adjuvant setting beyond 1 year of trastuzumab therapy.
  - In patients with early HR+/HER2+ breast cancer, within 1 year of trastuzumab therapy, neratinib treatment reduces the relative risk of relapse by 51% with an absolute benefit of 4.5% at 2 years of follow-up.[1]
  - These results are durable to 5 years with a 42% reduction in the risk of relapse and an absolute benefit of 5.1%.[52,84]
- Neratinib, with prophylaxis for diarrhoea, has a predictable and manageable safety profile.[56] Diarrhoea is a common side effect of adjuvant therapies for breast cancer, and neratinib-associated diarrhoea is an expected on-target side effect of an EGFR-targeted agent.[85-89] Diarrhoea was the most common TEAE in ExteNET, in which no protocol-mandated antidiarrhoeal prophylaxis was used. In CONTROL, structured prophylaxis with loperamide reduced the

incidence and duration of diarrhoea (14 days in CONTROL vs. 59 days in ExteNET).[50] UK clinicians confirmed that use of loperamide would be standard antidiarrhoeal prophylaxis in the UK (Appendix M). As demonstrated in CONTROL, this TEAE is manageable with proactive antidiarrhoeal prophylaxis, which is highlighted in the product label. The label indicates that patients are instructed to start antidiarrhoeal prophylaxis with the first dose and maintain regular dosing of the antidiarrhoeal product during the first 1 to 2 months of treatment, titrating to one to two bowel movements per day.[1]

- Unlike other agents used to treat early breast cancer, neratinib does not have cumulative or irreversible toxicities or toxicities associated with increased healthcare resource use such as neutropenia, neuropathy, and cardiac toxicity.[88]
- Neratinib has activity in both HR+/HER2+ and HR–/HER2+ breast cancer cell lines,[4] but bidirectional cross talk between ER and HER2 signalling pathways may explain enhanced efficacy of neratinib in HR+/HER2+ tumours. In HR+ tumours, preclinical results suggest that the dual blockade of ER and HER2 signalling pathways by neratinib results in enhanced and sustained anti-tumour activity. HER2 activation is recognised as a mediator of endocrine resistance, but inhibition of HER2 can reactivate ER signalling. Increased ER signalling can then provide an escape mechanism causing development of resistance to HER2-directed treatment.[5,6]

B.2.13.1 Strengths and limitations of the clinical evidence base for neratinib

The key clinical evidence for neratinib comes from ExteNET, a large international multicentre randomised placebo-controlled clinical trial, which included 13 sites in the UK. ExteNET is ongoing, but 5-year follow-up data are available, providing high-quality long-term evidence of the treatment effect of neratinib in patients with HR+/HER2+ breast cancer and who have completed a course of trastuzumab-based therapy less than 1 year ago.[47,52]

B.2.13.1.1 Internal validity of ExteNET and CONTROL

ExteNET is the only phase 3 RCT that compares neratinib with placebo. As there are no other HER2-directed therapies for early breast cancer used routinely in the extended adjuvant setting in the UK NHS, placebo is an appropriate comparator. A quality assessment of this RCT (see Section B.2.5 and Appendix D) determined the trial to be at a low risk of bias, with a robust overall design and execution, according to the NICE criteria for assessment and risk of bias.[67]

CONTROL is an open-label phase 2 cohort study. A quality assessment of this cohort (see Section B.2.5 and Appendix D) determined the trial to be at a low risk of

bias, with a robust overall design and execution, according to Critical Appraisal Skills Programme (CASP) criteria.[68]

B.2.13.1.2 External validity of ExteNET and CONTROL

While HR+ and time from completion of trastuzumab therapy were separate prespecified subgroups and stratification variables in ExteNET, the label population (patients with HR+/HER2+ breast cancer ≤ 1 year from trastuzumab) was not a prespecified subgroup in ExteNET. However, a large proportion (47%) of the ExteNET population met the label criteria, and additional efficacy and safety analyses for the label subgroup were conducted. Although additional safety subgroup analyses have not been conducted in CONTROL, the safety population was more reflective of the label than ExteNET, with a higher proportion of HR+ patients and very few patients initiating neratinib more than 1 year from trastuzumab.

The primary endpoint in ExteNET was iDFS, which is a frequently used endpoint in early breast cancer clinical trials in the adjuvant setting. According to US Food and Drug Administration guidance on clinical trials, iDFS is an acceptable surrogate endpoint in the adjuvant setting.[90] As patients with early breast cancer have low mortality rates, demonstrating OS in the adjuvant setting requires large patient populations and/or longer follow-up to show statistically significant differences between groups. In addition, it is challenging to incorporate the heterogeneity of treatments patients receive in the metastatic setting that may confound any eventual observed OS findings. Overall survival data from ExteNET are not yet mature and are powered for the ITT population, not the label population (final analysis for the ITT population will be at 248 events). Data for the HR+ subset < 1 year from trastuzumab will only be available from [redacted] and the sponsor/Puma remains blinded until then; it may be [redacted] until this endpoint is reached.

The ExteNET trial included 80 patients at 13 sites in the UK where neratinib was used in a research setting within UK NHS hospitals; therefore, results should be generalisable to UK clinical practice. As neratinib is administered orally for 1 year after routine trastuzumab-based therapy, the addition of 1 year of oral therapy should be easily integrated into routine UK clinical practice.

The original cohorts of CONTROL did not include any European sites, but cohorts in recruitment include sites in Spain. However, the antidiarrhoeal prophylaxis regimens used in the study (such as loperamide) are commonly used in UK clinical practice to treat chemotherapy-induced diarrhoea, so results are generalisable to the UK (Appendix M).

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was undertaken to identify all cost-effectiveness studies relevant to the decision problem from the published literature. A total of 21 economic evaluation studies were identified, including 5 health technology assessment (HTA) submissions. No economic evaluation of neratinib was identified from the review. Table 28 presents the summary of the HTA submissions that were deemed relevant to the submission. The full results of published economic evaluations that were included in the SLR along with details of the search strategy and study selection process are presented in Appendix G.

Table 28. Summary of the included health technology assessments

Intervention	Comparator	HTA Agency	Decision
Trastuzumab and standard adjuvant treatment	Standard adjuvant treatment alone	NICE (2006)[91]	Recommended as a treatment option for women with early-stage HER2+ breast cancer following surgery
Subcutaneous trastuzumab injection	Intravenous trastuzumab	SMC (2013)[92]	Accepted for use in line with previous SMC advice for intravenous trastuzumab
Trastuzumab plus adjuvant therapy	Adjuvant therapy alone	SMC (2006)[93]	Accepted for restricted use as a treatment for patients with HER2+ early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy (if applicable)
Pertuzumab in combination with trastuzumab and chemotherapy	Trastuzumab and chemotherapy	NICE (2018)[94] TA10184	In progress Indication: adjuvant treatment of early HER2+ breast cancer

Abbreviation: HER2+, human epidermal growth factor receptor 2-positive; HTA, health technology assessment; SMC, Scottish Medicines Consortium.

Full details of the search strategy, study selection process, and results are presented in Appendix G.

B.3.2 Economic analysis

The de novo economic model developed for the submission and the rationale for the model development are described below.

B.3.2.1 Patient population

The economic evaluation considers neratinib for extended adjuvant treatment of adult patients with early-stage HR+, HER2-overexpressed/amplified breast cancer and who are less than 1 year from the completion of prior adjuvant trastuzumab-

based therapy, which is consistent with the subgroup of the study population of ExteNET and the decision problem presented in Section B.1.1.

B.3.2.2 Model structure

Several different modelling approaches were considered during the development of the model structure for the neratinib economic evaluation. Partitioned survival models are used routinely in economic evaluations in oncology and have been the most commonly used in NICE appraisals.[95] However, the use of partitioned survival models has also recently been critiqued by the NICE Decision Support Unit (DSU). The challenge of using a partitioned survival model for this economic evaluation is that no OS data are available by treatment arm. Thus, data that would allow for estimation of full health-state occupancy by treatment arm are not available. Different approaches for modelling were considered, including modelling OS using correlation between iDFS and OS, but all were found to have limitations. To assess whether DFS can be used as a surrogate endpoint for OS, the following three requirements has been proposed to be met:[96] (1) evidence of strong correlation between DFS and OS (individual-level association); (2) evidence of a strong correlation between treatment effect on DFS and treatment effect on OS (trial-level association); and (3) clinical input on anticipated relationship between DFS and OS. We performed an analysis to consider whether a strong correlation between the treatment effect on DFS and the effect of treatment on OS could be identified. The approach was based on scatterplots between ln(HR DFS) and ln(HR OS) ($r = 0.2$) considering all trials of trastuzumab-containing regimens for early breast cancer included in a recent Cochrane review.[97] A strong relationship could thus not be identified. Therefore, extreme scenarios—for example, assuming the treatment effect on OS to be equal to the treatment effect on iDFS or assuming no treatment benefit on OS—were considered. However, both of these scenarios were considered to be unrealistic. It was clear that iDFS and OS are not fully correlated; thus, assuming equal treatment effect would likely have overestimated the effect of neratinib. Similarly, recurrence of disease—specifically distant recurrence—is known to have a significant impact on expected survival; therefore, assuming that a reduced number of recurrences as a function of improved iDFS would not lead to any survival benefits seems equally unrealistic.

Following consideration of the above challenges that would be associated with a traditional partitioned survival analysis approach, other potential modelling approaches were reviewed. These included the Markov model structure developed for the ongoing NICE appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer.[94] The model structure used for the pertuzumab economic evaluation included seven health states (iDFS on treatment, iDFS off treatment, non-metastatic recurrence, remission, first-line metastatic breast cancer, second-line metastatic

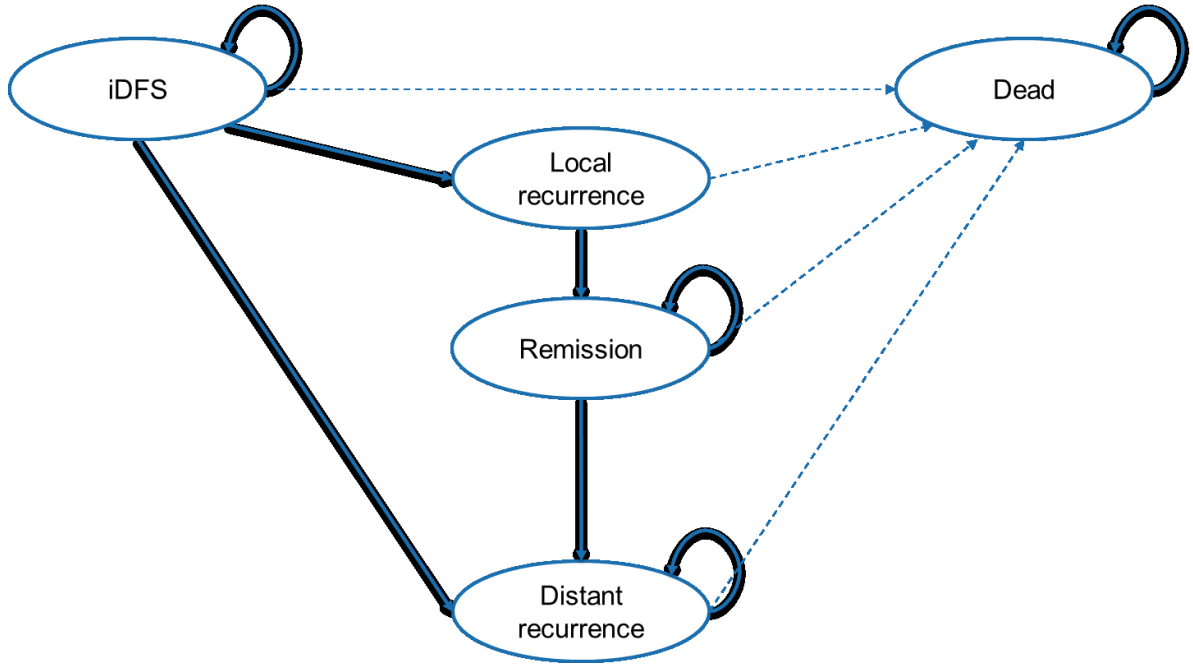
breast cancer, and death). The Evidence Review Group (ERG), clinicians consulted as part of the appraisal, and the appraisal committee for pertuzumab for adjuvant treatment of early HER2+ breast cancer considered the company's model structure to be appropriate in general and to be in line with the NICE reference case.

For the current submission, a five-health-state Markov model similar to that of the pertuzumab appraisal was developed to evaluate the incremental cost-effectiveness of neratinib versus standard treatment with no further HER2-directed therapy.

Figure 26 shows the five-health-state model structure. The five health states represent the primary stages of disease in early-stage breast cancer: disease free, local recurrence, remission, distant recurrence, and dead. General mortality data are applied to all health states apart from distant recurrence. It is assumed that all patients who die from breast cancer move through the distant recurrence health state before transitioning to the dead health state. This aligns with the economic evaluation developed for the ongoing NICE appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer and was seen to be reasonable by the ERG.[94]

The model health states correspond to the primary and secondary endpoints in the ExteNET trial as outlined in Section B.2.3.1.1. The model structure allows for variation in risk of recurrence and death over the time horizon, as observed in iDFS data from ExteNET for these patients.[48]

Figure 26. Overview of the five-health-state model structure



Abbreviation: iDFS, invasive disease-free survival.

Patients enter the iDFS health state and are treated with neratinib or given no treatment (placebo). Patients remain in the iDFS health state until they experience an iDFS event, local or distant recurrence, or death. After local recurrence, patients enter a tunnel health state in which they receive adjuvant therapy before they transition to either remission or death. For patients with locally recurrent disease who transition to remission, in line with ID1192, the model assumes that all patients progress to distant recurrence or die from general population mortality.

Patients experiencing distant recurrence while in iDFS transitioned directly to the distant recurrence health sate. No further explicit submodelling of progression-free survival or OS, dependent on line of therapy, was included in the distant recurrence health state.

From all health states, patients could transition to death. From the iDFS, local recurrence, and remission health states, patients were subject to all-cause mortality. Patients in distant recurrence were subject to postdistant recurrence mortality based on blinded survival data for both arms of ExteNET (see Section B.3.3.5).

Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and quality-adjusted life-years (QALYs) per cycle. A model cycle length of 1 month was selected to provide precision in tracking the number of patients in each health state over time, and a half-cycle correction was incorporated.

Treatment costs included costs of drug acquisition, administration, and monitoring. Costs and disutilities associated with AEs were estimated per episode and were applied once at the beginning of the simulation based on the proportion of patients in each treatment arm experiencing each AE. Costs and QALYs were discounted at 3.5% per annum, in accordance with the NICE reference case.[98]

Table 29 presents a summary of the core elements of the economic model compared with other relevant NICE appraisals.

Table 29. Features of the economic analysis

	Previous appraisals			**Current appraisal**	
Factor	**ID1192 NICE (2018)[94]**	**TA424 NICE (2016)[99]**	**TA107 NICE (2006)[100]**	**Chosen values**	**Justification**
Time horizon	52 years (lifetime)	50 years (lifetime)	45 years (lifetime)	55 years (lifetime)	In accordance with the NICE reference case[98]

	Previous appraisals			Current appraisal	
Factor	**ID1192 NICE (2018)[94]**	**TA424 NICE (2016)[99]**	**TA107 NICE (2006)[100]**	**Chosen values**	**Justification**
Treatment waning effect?	Effect maintained for 7 years before waning to null at 10 years	No waning Treatment effect set equal between arms after 7 years	Effect maintained for 10 years Two-thirds of this benefit is seen until year 45	Treatment effect maintained until hazard in iDFS state equal to general population hazard implemented in the base case	A maintained treatment effect was observed during the full 5-year follow-up in ExteNET Further detail given in Section B.3.3.1
Source of utilities	EQ-5D data collected during the APHINITY trial: ▪ Lloyd et al. (2006)[101]	Published literature: ▪ Lloyd et al. (2006)[101] ▪ Lidgren et al. (2007)[102]	Published literature	EQ-5D data collected during the ExteNET trial and published literature	In accordance with the NICE reference case[98]
Source of costs	Published literature and expert opinion	NHS reference costs, BNF, published literature, and expert opinion	MEDTAP study, ABACUS study, HERA database, and MIMS	NHS reference costs, BNF, published literature, and expert opinion	In accordance with the NICE reference case[98]

Abbreviations: ABACUS, Awareness and Beliefs About Cancer; BNF, British National Formulary; HERA, HERceptin Adjuvant trial; iDFS, invasive disease-free survival.

B.3.2.3 Intervention technology and comparators

The comparator in the economic analysis is standard treatment with no further HER2-directed therapy. As described in Section B.1.3.6, there are currently no treatment recommendations or approved biological therapies for people with HR+/HER2+ breast cancer in the extended adjuvant setting after 1 year of treatment with trastuzumab.

B.3.3 Clinical parameters and variables

B.3.3.1 Modelling of iDFS

It is common for oncology economic evaluations developed to support HTA submissions to only use parametric survival analysis fitted to data derived from pivotal trials for the interventions of interest and extrapolated over the full model time horizon. However, a large proportion of patients in the ExteNET trial remained disease free at the end of the 5-year follow-up (see Section B.2.6.1), and analysis of

the data suggested that hazard rates decreased over time (Appendix L, Section L6.1.1, Figure 9). Therefore, functions fitted to the trial iDFS data would not be expected to predict the increase in hazard at later times in the model because patients age and death from other causes makes an increasingly large proportional contribution to the risk of an iDFS event (noting that iDFS is defined as time to disease recurrence or death, whichever occurs first). In addition, more mature DFS data are available for patient cohorts with similar characteristics and treatment history to the control arm of ExteNET (e.g., from long-term follow-up of patients enrolled in trials investigating trastuzumab), which would be expected to be valuable in informing or validating iDFS predictions after the ExteNET trial follow-up. As a consequence, general population mortality data and external data for similar populations were both incorporated into the analysis.

A wide range of survival analyses were performed as described in detail in Appendix L. Standard analyses were performed to fit parametric functions to the ExteNET trial data as recommended in the NICE DSU guideline.[103] In addition, functions were fitted that incorporated more mature external DFS data and general population mortality rates, using methods proposed by Guyot et al. (2017)[104] and described in Jackson et al. (2017)[105].

Full description of these analyses can be found in Appendix L. Briefly, external data were sought to identify one or more studies with long-term DFS estimates for a population similar to that enrolled in ExteNET——specifically, patients with HR+ and HER2+ early breast cancer who were eligible for treatment with neratinib—who received standard of care in routine practice (see Appendix L, Section L.2.5). The SLR of the clinical literature performed for this appraisal identified one meta-analysis of RCTs presenting long-term follow-up of studies with patients treated with trastuzumab.[106] This publication presented a number of external data sources for DFS (see Appendix L, Section L.2.5.1). Data from the HERA trial[107] were determined to be the most appropriate for inclusion in the survival analysis because they were most closely aligned with clinical practice in the UK and because they were used in NICE TA107[99] and the updated trastuzumab economic analysis reported in Hall et al. (2011)[108]. Furthermore, HERA data were used for validation of extrapolations in the ongoing NICE appraisal of pertuzumab (ID1192).[94] External advisers also identified the HERA trial as the most appropriate data source for DFS. DFS data from HERA for HR+ patients with a median follow-up of 11 years reported by Cameron et al. (2017)[17] were used in the current survival analysis (presented in Appendix L, Section L.2.5.1, Figure 5B). The survival times from Cameron et al. (2017)[17] were adjusted so that the mean time since trastuzumab aligned with the ExteNET trial. As the Cameron et al. (2017)[17] data are also not yet mature (approximately 80% of patients are still at risk at the end of follow-up), further extrapolation was required beyond the

end of the HERA trial. Thus, OS for the general UK female population[109] was used for long-term extrapolation of the iDFS curve beyond the follow-up time of ExteNET and HERA.

In contrast to the approach taken in the ongoing NICE appraisal of pertuzumab (ID1192),[94] the current survival analysis did not incorporate a cure rate parameter. Although we fully agree that early-stage breast cancer is treated with curative intent, the cure rate introduced in the ongoing pertuzumab appraisal was included as an adjustment to extrapolations because of a poor fit to external data. As can be seen in the following sections, the survival analysis for the current submission did not have the same limitations, and estimates from the primary survival analysis of ExteNET combined with general population mortality aligned well with more complex models, which also directly incorporated HERA data. Thus, the proportion of patients being cured following treatment is expected to already be captured in the extrapolation of iDFS from ExteNET.

B.3.3.1.1 Survival analysis

A wide range of parametric and flexible survival models were fitted to each of the data sets used in the analysis; iDFS data from the ExteNET trial, identified external data for DFS from HERA, and general population mortality data separately. The steps followed to determine the most appropriate survival functions included the following (please see Appendix L for full details):

- Testing for proportional hazards between treatment arms in ExteNET:
  - Tests were performed to determine if the data from ExteNET indicate that proportional effects could be assumed. The test for non-proportional hazards (Therneau-Grambsch test) also was not significant (Chi-squared = 0.314, *P* = 0.575).
  - Because there was no evidence against the proportional hazard assumption for iDFS, a pooled survival model with a covariate for treatment effect was deemed appropriate for the ExteNET data.
- Fitting and selection of survival models for all data sets:
  - A range of survival models were fit to the data.
  - Within the various survival models, the Akaike information criterion (AIC), Bayesian information criterion (BIC), and Integrated Brier score (IBS) goodness-of-fit statistics were assessed to identify differences in statistical fit among the survival models.
  - The choice of survival model used for the base-case economic model was based on the following:

- ◊ Assessing the AIC, BIC, and IBS statistics of the survival models, which provides goodness of fit to the Kaplan-Meier data from ExteNET, HERA, and the general population
- ◊ Visual fit compared with the Kaplan-Meier data from ExteNET, HERA, and the general population

B.3.3.1.2 Selection of survival function data included in the model base-case analysis

Table 30 presents the base-case and scenario analysis functions selected to the ExteNET trial data, the HERA trial data, and the general population mortality data.

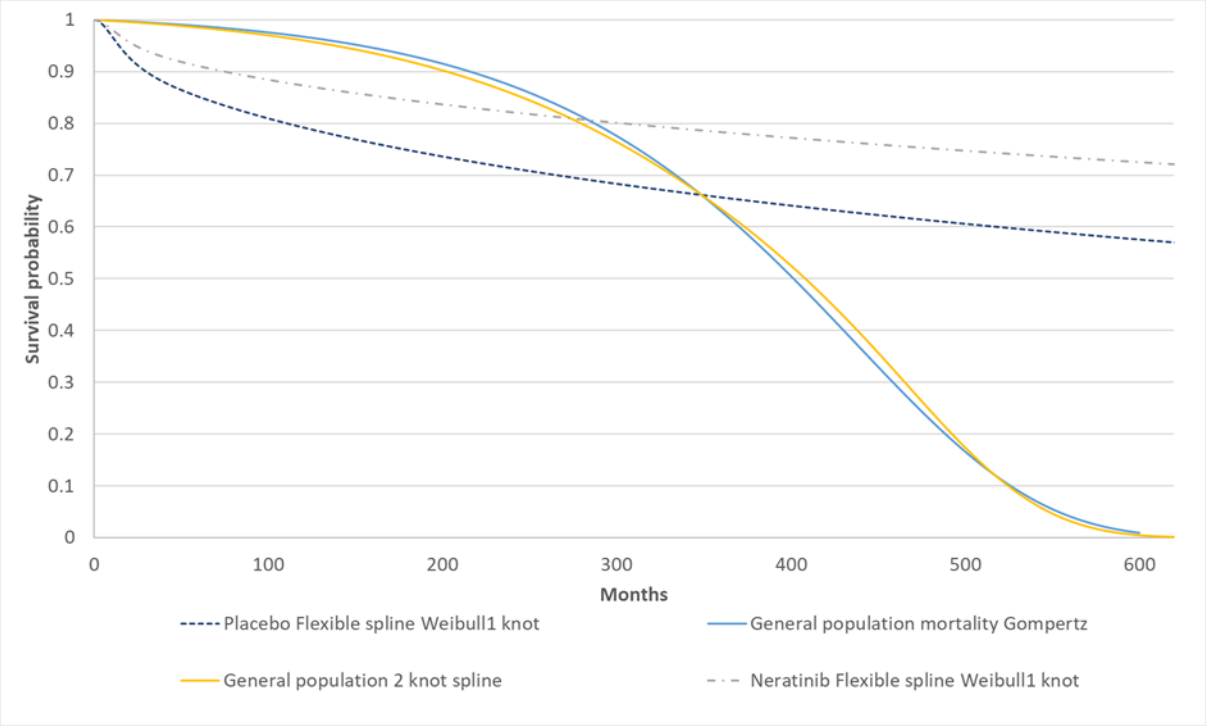
Table 30. Selected distributions for iDFS extrapolation

Data set	Distribution
ExteNET	
Base case	Flexible-spline Weibull 1 knot
Scenario	Gompertz
HERA	
Base case	Flexible-spline Weibull 2 knot
Scenario	Gompertz
General population mortality	
Base case	Flexible-spline Weibull 2 knot
Scenario	Gompertz

Abbreviations: HERA, HERceptin Adjuvant trial; iDFS, invasive disease-free survival.

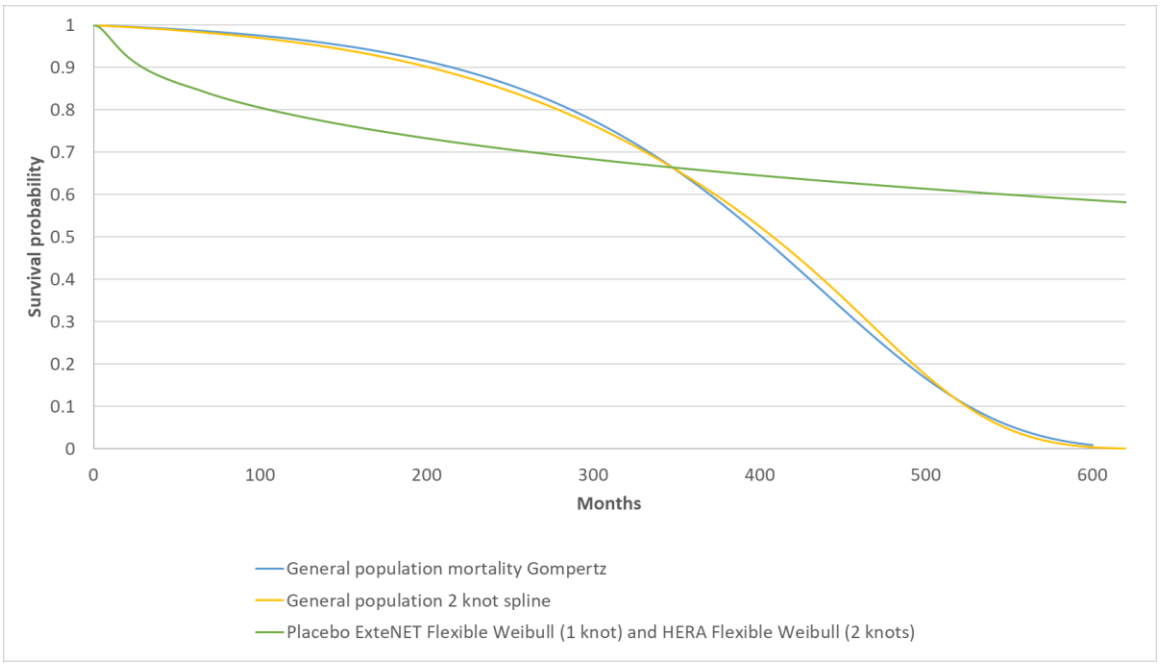
As expected, the extrapolated survival from the ExteNET and HERA studies resulted in a greater proportion of patients surviving than the general population from approximately month 300 to 350, depending on data and treatment arm (Figure 27 and Figure 28). Thus, it was confirmed that only using extrapolated iDFS from ExteNET or with the addition of the HERA data would not result in plausible long-term predictions of iDFS. This supports the inclusion of general population data in the analysis to avoid implausible extrapolation of long-term survival.

Figure 27. Plot of survival curves for iDFS fitted to ExteNET iDFS and general population survival data



Abbreviation: iDFS, invasive disease-free survival.

Figure 28. Plot of survival curves fitted to predicted iDFS by using HERA DFS data and general population survival data



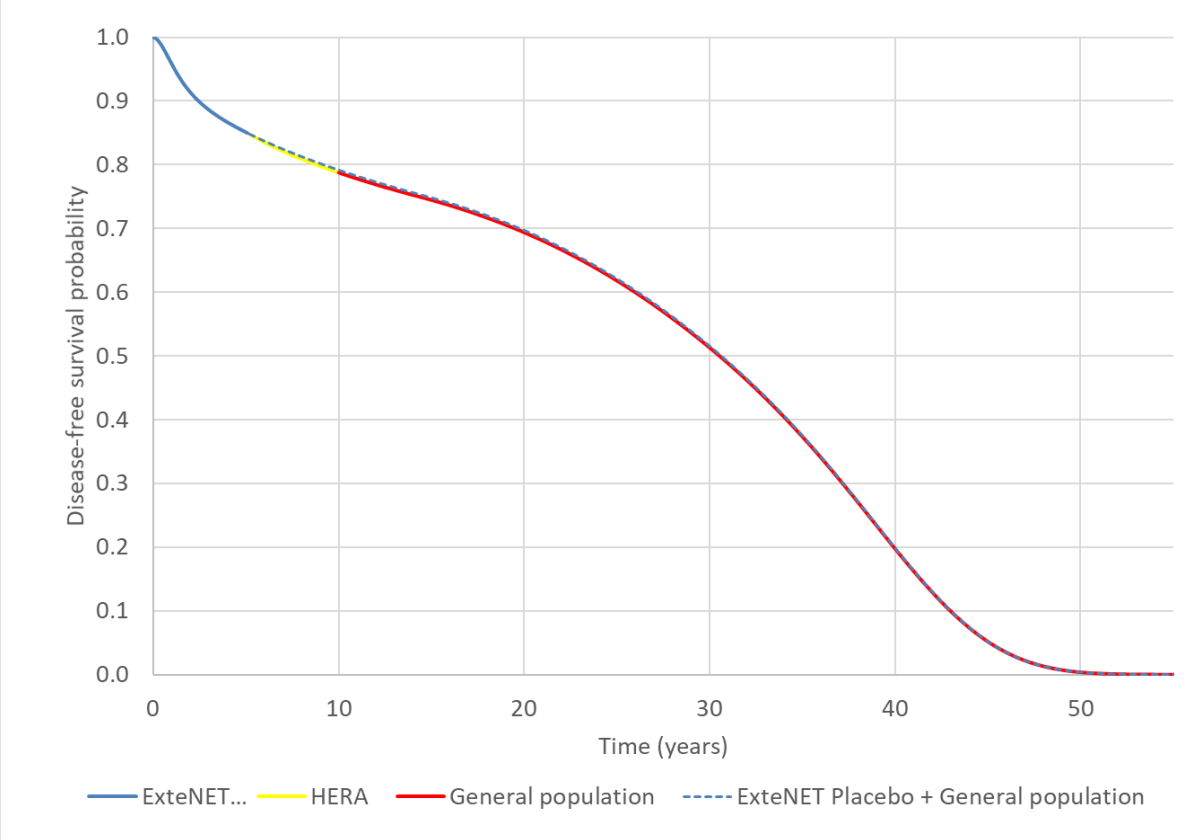
Abbreviations: HERA, HERceptin Adjuvant trial; iDFS, invasive disease-free survival.

As presented in Section B.3.3.1.1 and fully outlined in Appendix L, the intent at the onset of the survival analyses was to use all three data sets (ExteNET, HERA, and general population) to predict the long-term iDFS in line with the methods proposed

by Jackson et al. (2017)[105]. However, after performing all analyses, it was notable that the survival predictions based on the ExteNET and general population data only were highly consistent with predictions that also incorporated the HERA data. This is shown in Figure 29 in which survival curves composed of ExteNET placebo arm, HERA, and general population data are overlaid onto survival predictions from the ExteNET placebo arm and the general population. It is clear that the two approaches only lead to only marginally different survival predictions.

Adding the HERA data explicitly to the survival analysis extrapolation adds additional complexity and uncertainty (because it contributes another set of survival extrapolations to the analysis and is based on DFS rather than iDFS). Further, the HERA data represent the placebo arm well, but their relation to the neratinib arm is less clear and further adjustments would potentially be needed. Thus, the ExteNET data in combination with general population survival were used for the base-case extrapolation of iDFS in the model. Functions that incorporated the HERA data were used for validation and for supporting scenario analyses in the model. The notable close alignment of the extrapolation based on the ExteNET iDFS data with the more mature HERA DFS data provides important evidence for the validity of the extrapolation based on the ExteNET data on which the model is based.

Figure 29. Plot of base-case survival curves for predicted iDFS by using HERA data in addition to ExteNET data

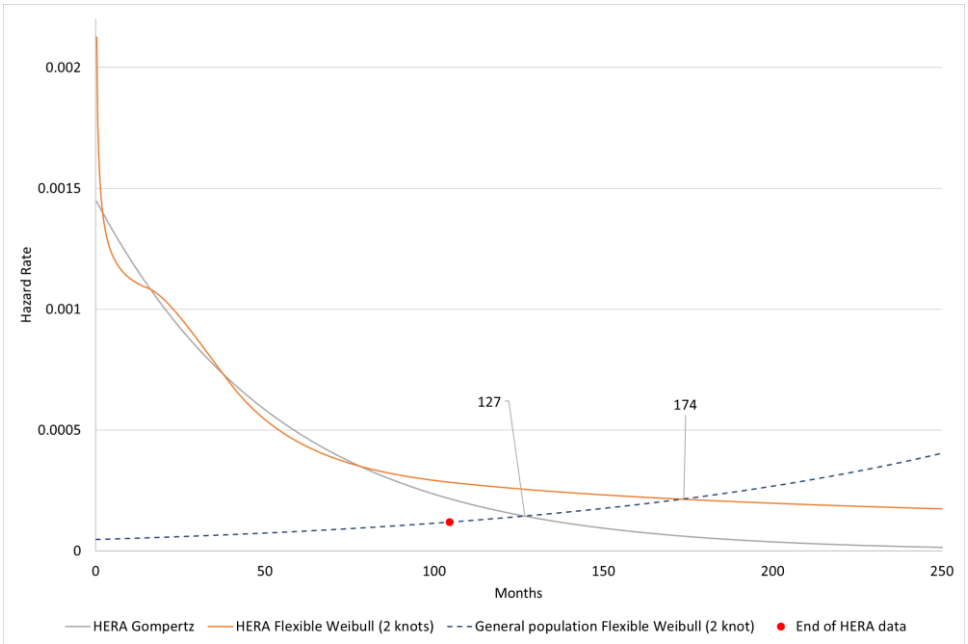


Abbreviations: HERA, HERceptin Adjuvant trial; iDFS, invasive disease-free survival.

B.3.3.1.3 Transition from ExteNET iDFS to general population mortality

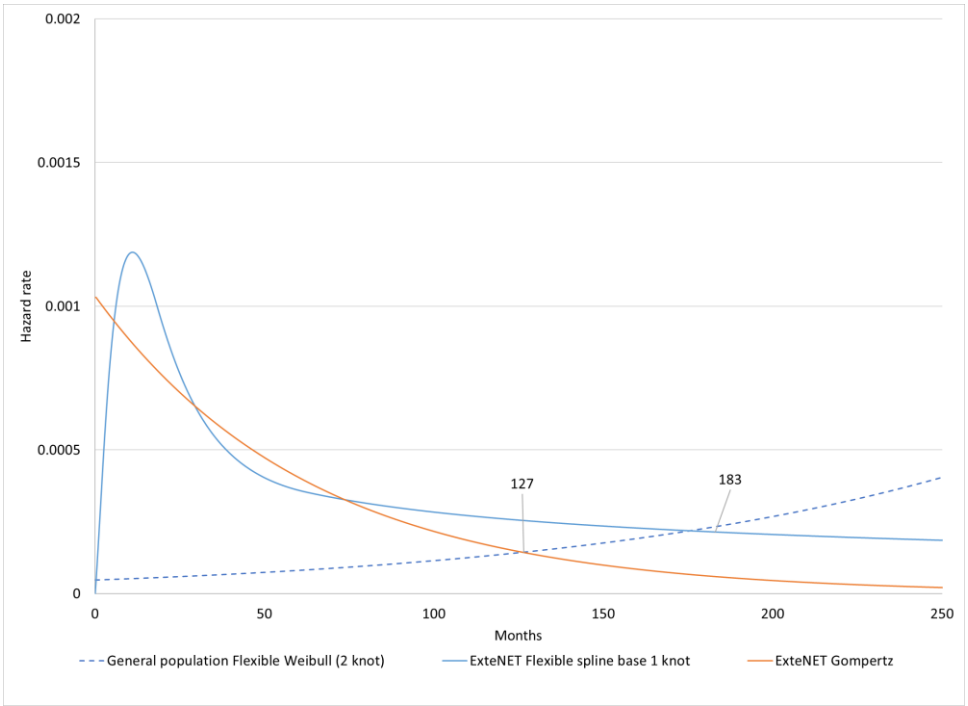
There is limited evidence available regarding the long-term risk of an iDFS event for the HER2/HR+ patient population and thus from what time point general population mortality would be reasonable to assume. A recent meta-analysis showed that, for patients with HR+ breast cancer, there is a continued risk of recurrence at 20 years after their initial breast cancer diagnosis.[25] To our knowledge, similar data are not available for the HER2/HR+ population, and the HR+ population data are likely not directly transferrable because of higher incidence of early recurrence in the HER2/HR+ population compared with the HR+ population. Clinical input sought by Puma on this matter indicated that, given the curative intent of the treatment and early recurrence in the HER2/HR+ population, it is plausible to assume that the iDFS risk would approach that of the general population at some point, although it is difficult to determine at what point. In the ongoing NICE appraisal of pertuzumab (ID1192),[94] the manufacturer claimed that the risk of an iDFS event at the end of the HERA trial was similar to that of the UK general population. The ERG for that appraisal was not able to verify that claim, but it was agreed that this was not an implausible assumption. The clinical input Puma has received confirmed that this is still uncertain, as there is not any evidence available to verify such a claim. Thus, we analysed the hazard over time from the HERA trial in relation to the UK general population mortality. As shown in Figure 30, the hazards rate at the end of the HERA trial (equal to 8.5 years after initiation of neratinib treatment) are still higher for the HERA population compared with that of the general population. Using the survival curves with best fit to the digitised DFS HERA data (as described above and in Appendix L), our analyses show that the risk of an DFS event is likely to be equal to that of the general population in a time span of approximately 125 to 175 months after initiation of neratinib treatment. Therefore, it seems plausible to assume an increase iDFS risk compared with the general population for a longer time period than the 10 years after initial breast cancer diagnosis cited in the ongoing NICE appraisal of pertuzumab (ID1192).[94] A similar pattern was seen in the extrapolated hazard rate for the placebo arm of ExteNET (Figure 31), which crosses the general population mortality hazards at approximately 125 to 185 months dependent on distributions used. Based on this analysis, switching from the ExteNET iDFS extrapolation to the general population mortality was implemented in the model so that extrapolations were based on ExteNET data until hazards for the general population exceeded that of ExteNET. This switch was dependent on the treatment arm to account for the differences in hazard rates between treatment arms for scenarios in which this would be relevant.

Figure 30. Comparison of hazard rates between HERA and general population mortality



Abbreviation: HERA, HERceptin Adjuvant trial.

Figure 31. Comparison of hazard rates between the placebo arm iDFS from ExteNET and general population mortality



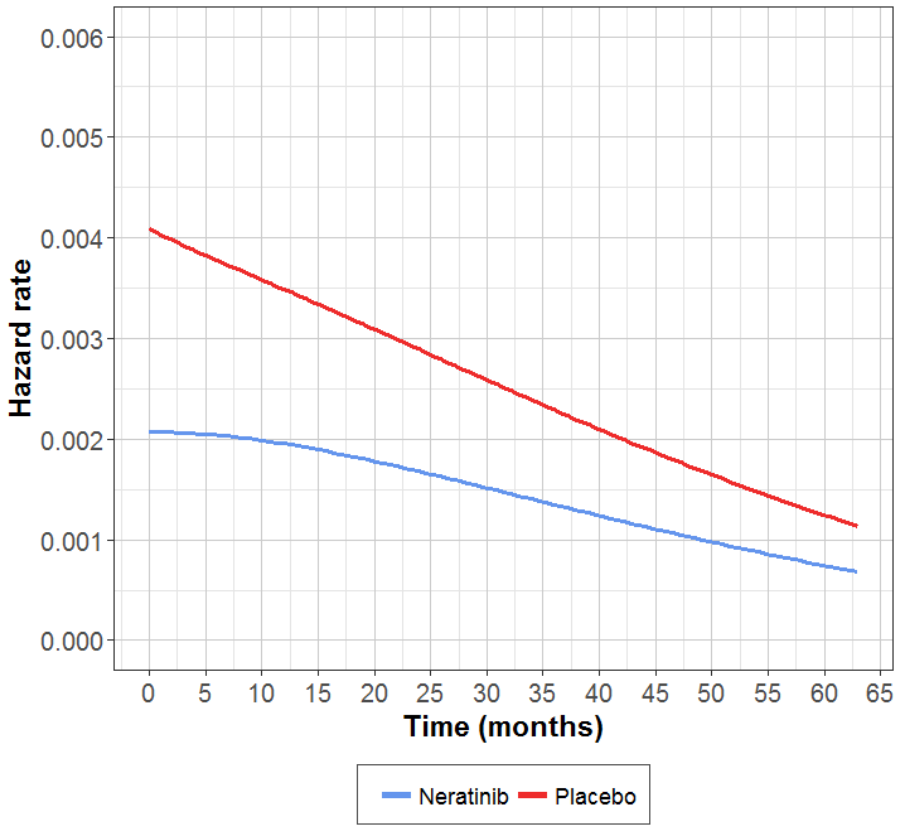
Abbreviations: HERA, HERceptin Adjuvant trial; iDFS, invasive disease-free survival.

B.3.3.1.4 Treatment effect beyond trial follow-up

During the 5-year follow-up in ExteNET, there was a clear continued treatment effect for the 4-year follow-up time after treatment (Figure 32). Therefore, it is clear that

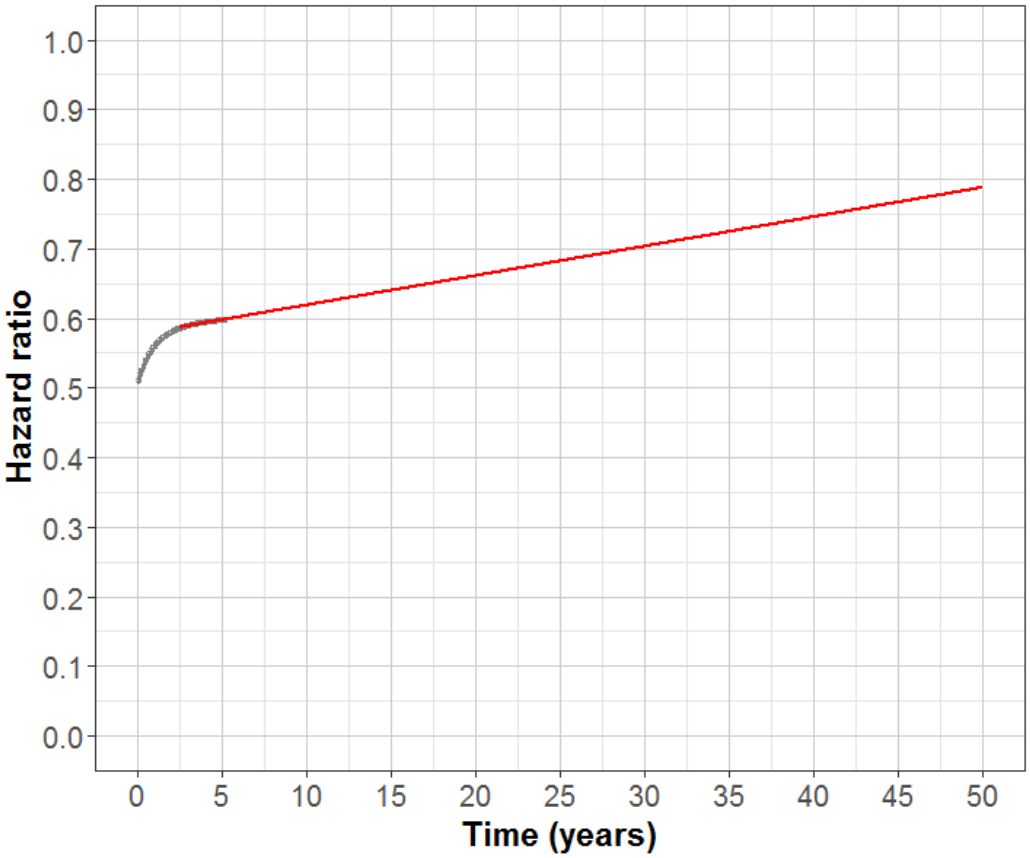
patients continue to benefit from the treatment well beyond 1 year of treatment. To determine the time frame for which treatment effect would be applied in the economic model, we extrapolated the hazard ratio with a linear regression beyond the trial to identify at what point it would reach a hazard ratio of 1. The predictions showed that at no point within the modelling time horizon would the hazard ratio reach 1 (Figure 33 and Appendix L, Section L.6.1.1) for the HR+ population.

Figure 32. Smoothed hazard rates for DFS from the ExteNET trial data: prior trastuzumab in HR+ population



Abbreviations: DFS, disease-free survival; HR+, hormone receptor-positive.

Figure 33. Hazard ratio plot for DFS derived from the smoothed hazard rates from the ExteNET data: prior trastuzumab in HR+ population



Abbreviations: DFS, disease-free survival; HR+, hormone receptor-positive.

Given the continued treatment effect shown during the trial and the lack of evidence of the treatment effect waning considerably towards the end of the trial, base-case analyses were based on the extrapolation of data from ExteNET without further adjustments of treatment effect beyond the trial time horizon. This leads to patients in the neratinib arm transitioning to general population mortality earlier than the placebo arm (e.g., year 12 vs. year 16 with the base-case distributions). As previously described, this is done to negate neratinib patients having a lower probability of an iDFS event than that of the general population. Thus, such a transition lessens the treatment effect compared with fully relying on the extrapolated survival from the trial.

A more rapid waning of treatment effect was explored in sensitivity scenarios, in which the treatment effect was tapered over a period of 8.65 years after the end of the trial. This trend was based on linear extrapolation of the hazard ratio in ExteNET for patients regardless of HR status (see Appendix L). However, given the smaller treatment effect seen for this population and lack of bidirectional cross talk between HR and HER2 signalling pathways that may explain the notable efficacy of neratinib

in HR+/HER2+ tumours, it may be reasonable to conclude that this could be seen as a conservative assumption.

B.3.3.2 Risk of death from all health states other than distant recurrence

As noted in Section B.3.2.2, it was assumed in the model that all breast cancer–related mortality would occur once patients had incurred a distant recurrence. Hence, for all other health states, the risk of dying was modelled through age-adjusted survival for the female general population.[109] This assumption was also supported by only 2 (0.3%) neratinib and 3 (0.5%) placebo patients experiencing death from any cause as an iDFS event during the 5-year follow-up period. Thus, it was considered more appropriate to base the non–cancer-related mortality on the age-adjusted survival for the female general population. The same assumption was also deemed plausible by the ERG for the ongoing NICE appraisal of pertuzumab (ID1192).[94]

B.3.3.3 Modelling of proportion of local and distant recurrence

The proportion of patients transitioning from iDFS to local or distant recurrence was derived from the ExteNET trial. A slight difference in the proportion of distant and other recurrences was observed between arms; thus, the observed proportions for each arm were included in the base-case analysis (Table 31). In the ongoing NICE appraisal of pertuzumab (ID1192),[94] the ERG argued for including proportions of distant events varying with time. However, it is not evident from comparing the 5-year data (Table 31) with the 2-year data cut (Table 32) that the proportion of site of recurrence varied over time; thus, proportions from the 5-year data were kept constant through the modelling time horizon.

Table 31. Type of iDFS event observed in ExteNET (5 years)

	Neratinib (n = 670)	**Placebo (n = 664)**
Patients with events, n (%)	51 (7.6)	89 (13.4)
Local/regional invasive recurrence	5 (0.7)	18 (2.7)
Invasive ipsilateral breast tumour recurrence	2 (0.3)	5 (0.8)
Invasive contralateral breast cancer	2 (0.3)	5 (0.8)
Distant recurrence	40 (6.0)	63 (9.5)
Death from any cause	2 (0.3)	3 (0.5)
Patients censored, n (%)	619 (92.4)	575 (86.6)
Proportion distant recurrence, n (%)	40/49 (81.6)	63/91 (69.2)
Proportion other recurrences, n (%)	9/49 (18.4)	28/91 (30.8)

Abbreviation: iDFS, invasive disease-free survival.

Source: Puma data on file (2018)[72]

Table 32. Type of iDFS event observed in the ExteNET trial (2 years)

	Neratinib (n = 670)	Placebo (n = 664)
Patients with events, n (%)	26 (3.9)	55 (8.3)
Local/regional invasive recurrence	3 (0.4)	12 (1.8)
Invasive ipsilateral breast tumour recurrence	1 (0.1)	2 (0.3)
Invasive contralateral breast cancer	1 (0.1)	2 (0.3)
Distant recurrence	20 (3.0)	38 (5.7)
Death from any cause	1 (0.1)	1 (0.2)
Patients censored, n (%)	644 (96.1)	609 (91.7)
Proportion distant recurrence, n (%)	20/25 (80.0)	38/54 (70.4)
Proportion other recurrences, n (%)	5/25 (20.0)	16/54 (29.6)

Abbreviation: iDFS, invasive disease-free survival.

Source: Puma data on file (2018)[71]

B.3.3.4 Local recurrence pathway

The modelling of local recurrence was aligned with the approach and assumptions used in the ongoing NICE appraisal of pertuzumab (ID1192).[94]

B.3.3.4.1 Local recurrence

It was assumed that all patients who experience a local recurrence would undergo 1 year of additional adjuvant therapy before they transition into the remission health state or die due to all-cause mortality. It was assumed that all patients with local recurrence would reside in the health state for 12 months before being able to transition to remission after additional adjuvant therapy. As acknowledged both in the company submission and the ERG report for NICE appraisal ID1192,[94] this might not be completely realistic; in reality, some patients may experience metastases during this 12-month treatment period. However, it was also agreed that this was a reasonable assumption and thus has been used in the current model base case; the impact of this assumption was tested in scenario analyses.

B.3.3.4.2 Remission

Patients who have completed adjuvant therapy in the local recurrence state and who have not died due to all-cause mortality transition to the remission state after 12 months. When in remission, patients can either die from all-cause mortality or experience another recurrence.

As with NICE appraisal ID1192,[94] it is assumed that any recurrence from remission would be distant in nature, as a patient in remission will have already experienced a

local recurrence. Further, the same monthly transition probability of 0.00757 for transitioning from remission to distant recurrence, as used in ID1192[94] and TA424[99], was included in the current analysis and assumed to be constant with time. That transition probability was obtained from a study by Hamilton et al.[110], which included a cohort of 12,836 patients with early breast cancer and reported the estimated risk of incurring a second malignancy following adjuvant therapy.

B.3.3.5 Distant recurrence

Patients entering the distant recurrence health state in the model are assumed to receive an average of two lines of subsequent therapy before eventually transitioning to death. Inclusion of two lines of subsequent therapy was based on clinical input and the approach taken in the ongoing NICE appraisal of pertuzumab (ID1192).[94] However, contrary to the model used for pertuzumab, the current model did not explicitly model the PFS and OS associated with the individual subsequent therapies. As neratinib is not approved in metastatic breast cancer, the subsequent treatment will not be influenced by neratinib treatment for early breast cancer; thus, it was seen as unnecessarily complicated to model postdistant recurrence survival (PDRS) specifically for each treatment. Rather, subsequent treatment was modelled by including the cost of the different subsequent treatments and using PDRS from the ExteNET trial. The approach taken in the ongoing NICE appraisal of pertuzumab (ID1192),[94] which specifically modelled survival when in distant recurrence based on trial data from subsequent lines of therapy, was also criticised by the ERG for that submission because it produced ill-fitting OS models compared with the OS observed in the pertuzumab clinical trial. Thus, using PDRS from ExteNET was deemed to better represent the expected survival for the patient population. The model was programmed to allow the risk of death for patients with distant recurrence to vary with time since their recurrence, based on survival functions fitted to the PDRS data from ExteNET. This overcomes the limitation of only being able to use an exponential distribution with a constant hazard to model PDRS, as done and critiqued in the ongoing NICE appraisal of pertuzumab (ID1192),[94] but allows for a full range of distributions to be explored.

B.3.3.5.1 Distant recurrence survival

Mortality from distant recurrence was modelled using the blinded PDRS for both arms of the ExteNET trial with survival models fitted to extrapolate survival beyond the study time horizon. Figure 34 shows the cumulative survival plot of PDRS for all patients experiencing a distant recurrence in ExteNET.

Figure 34. ExteNET: Kaplan-Meier curve of blinded PDRS, HR+ population ≤ 1 year from prior adjuvant trastuzumab

Abbreviations: HR+, hormone receptor-positive; PDRS, postdistant recurrence survival.
Source: Puma data on file (2018)[111]

TTDR has previously been shown to have an impact on expected PDRS.[112,113] Thus, we investigated the impact of TTDR on PDRS from ExteNET. Figure 35 shows the survival stratified by year of recurrence from randomisation; it is clear that patients with a recurrence within the first year since randomisation appear to have a poorer prognosis than those with a later recurrence. However, there does not appear to be a clear differentiation between time categories of recurrence beyond the first year of ExteNET. This corresponds well to cutoff points previously used in which a 24-month metastatic-free interval from disease onset had been used,[113] which would equal 12 months after start of neratinib.

To account for the impact of timing of recurrence in the model, additional analyses of PDRS were performed using different survival curves for PDRS for patients experiencing distant recurrence ≤ 12 months versus > 12 months from randomisation (Figure 36).

Figure 35. ExteNET: Kaplan-Meier plot of analysis of overall survival postdistant recurrence for HR+ patients who completed trastuzumab ≤ 1 year by time of distant recurrence, ITT population

Abbreviations: HR+, hormone receptor-positive; ITT, intention to treat.

Source: Puma data on file (2018)[114]

Figure 36. ExteNET: Kaplan-Meier plot of analysis of overall survival postdistant recurrence for HR+ patients who completed trastuzumab ≤ 1 year and had distant recurrence ≤ 12 months vs. > 12 months from randomisation, ITT population

Abbreviations: CI, confidence interval; HR+, hormone receptor-positive; ITT, intention to treat; NE, not estimable.

Source: Puma data on file (2018)[115]

Survival analyses

The process for fitting survival models to patient-level data was based on methods guidance from the DSU at NICE.[103] The choice of survival model was based on the AIC and BIC statistics of the survival models, which provide goodness of fit to the Kaplan-Meier data from ExteNET and visual fit compared with the Kaplan-Meier data from ExteNET.

Table 33 summarises the AIC and BIC values for the survival models explored for PDRS. The exponential distribution provided the lowest AIC and BIC followed by Gompertz distribution. Differences in AIC and BIC were comparatively small between exponential and Gompertz distributions based on a 3 to 5 difference in AIC/BIC. Thus, the selection of which of the two curves should be used as the base-case distribution was guided based on the visual fit. As shown in Figure 37, the Gompertz distribution produced a slightly better visual fit to the data compared with the exponential distribution and therefore was selected for the base-case analysis.

Table 33. Summary of goodness-of-fit data for survival models for PDRS

Distribution	AIC	BIC
Exponential	**261.02**	**263.71**
Gompertz	**261.44**	**266.82**
Gamma	262.69	270.77
Weibull	262.83	268.21
Logistic	267.36	272.74
Lognormal	274.06	279.44

Abbreviations: AIC, Akaike information criterion, BIC, Bayesian information criterion; PDRS, postdistant recurrence survival.

Figure 37. Plot of survival curves for PDRS compared with ExteNET Kaplan-Meier curves

Abbreviation: PDRS; postdistant recurrence survival.

Source: Puma data on file (2018)[115]

Table 34 and Table 35 summarise the AIC and BIC values for the survival models explored for PDRS for time of recurrence ≤ 12 months versus > 12 months from randomisation. Based on the AIC and BIC, the same functions provided the best fit as those models fitted to the data not split by time of recurrence, specifically exponential distribution followed by Gompertz. Differences in AIC and BIC were smaller between exponential and Gompertz distributions than what would generally be considered a relevant difference. As shown in Table 34, the Gompertz distribution produced a better visual fit to the data compared with the exponential distribution for patients experiencing a recurrence after 1 year; therefore, Gompertz was the preferred distribution for this extrapolation. For the patients experiencing recurrence ≤ 12 months from randomisation, the visual fit of exponential and Gompertz distributions was almost identical, and selection for this subgroup would have marginal impact on the results. For consistency with the subgroup > 12 months, the Gompertz survival functions also were selected for the subgroup ≤ 12 months.

Table 34. Summary of goodness-of-fit data for survival models for PDRS > 12 months from randomisation

Distribution	AIC	BIC
Exponential	**177.78**	**180.20**
Gompertz	**177.53**	**182.37**
Gamma	179.57	186.83
Weibull	179.24	184.08
Logistic	182.10	186.93
Lognormal	188.10	192.94

Abbreviations: AIC, Akaike information criterion, BIC, Bayesian information criterion; PDRS, postdistant recurrence survival.

Source: Puma data on file (2018)[116]

Table 35. Summary of goodness-of-fit data for survival models for PDRS ≤ 12 months from randomisation

Distribution	AIC	BIC
Exponential	**81.30**	**82.56**
Gompertz	**83.30**	**85.81**
Gamma	85.07	88.84
Weibull	83.22	85.73
Logistic	84.76	87.28
Lognormal	85.50	88.02

Abbreviations: AIC, Akaike information criterion, BIC, Bayesian information criterion; PDRS, postdistant recurrence survival.

Source: Puma data on file (2018)[116]

Figure 38. ExteNET: plot of survival curves for overall survival postdistant recurrence > 12 months and ≤ 12 months from randomisation compared with ExteNET Kaplan-Meier curves

Source: Puma data on file (2018)[116]

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

HRQoL data were collected in ExteNET using the EQ-5D-3L preference-based health-state utility questionnaire (EQ-5D Utility Index) at baseline and months 1, 3, 6, 9, and 12 (end of treatment) for patients on treatment[51,53,54] (see Section B.2.6.1.4). Patients discontinuing or experiencing a recurrence were not followed up with further with regards to EQ-5D. Utility scores were based on a UK value set.[117]

The main objective of the utility analysis was to generate estimates of utility (EQ-5D Index score) for each of the health states in the economic model. Descriptive summaries of utilities over time, by diarrhoea grade and treatment group, were considered. Utility values were not collected after recurrence; as such, the utility analysis considered utility values for patients in iDFS. Minimal data were available for patients with a recurrence (11 patients had utility data after recurrence), and the remainder of the description of methods and results for the ExteNET trial included only utility data for iDFS. 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], respectively), which would be expected owing to randomisation to treatment arms.

To appropriately consider utilities over time and account for correlations between repeated utility values at different time points for the same patient, a generalised linear mixed model was fitted to the data using xtmixed in Stata, with utility index postbaseline as the dependent variable. The results were independently quality-control checked using proc mixed in SAS. The analysis considered ExteNET data from the primary population of interest, patients with HR+, HER2+ breast cancer who have completed a course of adjuvant trastuzumab less than 1 year ago. Within the mixed model, a number of fixed effects were considered. The model was then reduced using a stepwise approach to a final, more parsimonious model that forced the inclusion of diarrhoea grade (considered as a categorical covariate) and included other covariates that were significant in the model.

The following fixed effects were initially considered: diarrhoea grade, treatment, month of visit, age, baseline utility, baseline Eastern Cooperative Oncology Group (ECOG), nodal status, and concurrent versus sequential trastuzumab. Patient was included as a random effect in the model. Also, an interaction between diarrhoea grade and visit was considered to explore whether there was evidence that the impact of diarrhoea on utilities changed over time. In addition to generalised linear mixed model, generalised estimating equation was also explored. However, as anticipated, the results were highly comparable. There was some indication of a difference in utility by month of visit; however, the pattern was not clear (and, based on a likelihood ratio test, month of visit was not significant over all in the model). Results from a model, including month of visit in addition to age, baseline utilities, and sequential/concurrent trastuzumab, produced highly similar values to those from the final model. The final model included fixed effects for age, baseline utility index, and sequential/concurrent trastuzumab, and a marginal and a random effect for patient (with utility as the dependent variable). A model considering change in utility index as the outcome variable was also performed, and estimated utilities from this model were similar to those in the final model.

Marginal means were created based on the final model. The results from this analysis did not follow an anticipated pattern: there was a lower utility value for those with a diarrhoea grade 0 compared with those with a diarrhoea grade 1 and 2. One possibility for the unexpected results may be missing data; as such, the results from this utility analysis, which assumed data were missing at random, should be interpreted with caution.

The mean utility estimates based on the mixed model are shown in the table below, these are presented at the means of the other covariates in the model.

Table 36. Summary of utility values based on mixed model of data from ExteNET

State	Utility value: mean (standard error)	95% confidence interval
No diarrhoea	0. 837 (0.004)	0.829-0.846
Grade 1 and 2 diarrhoea	0.839 (0.005)	0.829-0.849
Grade 3 diarrhoea	0.827 (0.009)	0.810-0.844

B.3.4.2 Mapping

EQ-5D data were collected in the ExteNET study in line with the NICE reference case. Utility values for health states and AEs for which ExteNET data could not be used were obtained from the literature. Therefore, there was no need to use mapping techniques.

B.3.4.3 Health-related quality of life studies

An SLR was undertaken to identify HRQoL studies relevant to the decision problem from the published literature. The SLR was performed using the inclusion and exclusion criteria defined in Appendix G and the search strategy presented in Appendix H.

B.3.4.3.1 Summary of identified studies and results

This SLR identified five studies reporting health-state utility estimates in patients with HER2+ breast cancer. Because there were so few studies identified reporting health-state utilities for the patient population of interest, the identified economic evaluations of treatments in HER2+ early breast cancer were also used to inform the selection of relevant utility estimates and resulted in the identification of 14 studies reporting HRQoL data (presented in Appendix H).

One source of utility values was identified from the SLR[102] and additional reviews of recent NICE submissions in similar indications were used to inform the selection of utility values in metastatic recurrence, which was outside the scope of the SLR, resulting in the identification of Lloyd et al. (2006)[101], a source widely used and accepted in previous NICE submissions.

B.3.4.4 Adverse reactions

Adverse reactions were experienced by almost all patients in the label safety population study (neratinib arm, 98.0%; placebo arm, 86.3%),[52] while TEAEs categorised as serious were roughly equal between arms (neratinib, 6.8%; placebo, 5.5%).[52]

Diarrhoea was the most common TEAE in the entire safety population (neratinib, 95.4%; placebo, 35.4%)[82] and the label safety population (neratinib, 93.7%; placebo, 28.2%).[83] Diarrhoea is an expected on-target side effect of an EGFR-targeted agent. In the safety population, grade 3 diarrhoea occurred after a median of 8 days (IQR, 4-33 days) and lasted a median of 5 days (IQR, 2-9 days) per patient. Most grade 3 diarrhoea events occurred in the first month of treatment (see Section B.2.10).

In the safety population, 55.5% in the neratinib group versus 33.8% in the placebo group had grade 1-2 diarrhoea; 39.9% in the neratinib group versus 1.6% in the placebo group had grade 3 diarrhoea; and 1 patient (< 1%) in the neratinib group versus none (0%) in the placebo group had grade 4 diarrhoea (Table 37).[48] Apart from GI events, all other grade 3-4 AEs occurred in fewer than 2% of neratinib-treated patients (Table 38). Table 37 presents diarrhoea episodes.

Table 37. Diarrhoea episodes in ExteNET

Adverse event	Incidence	Events (mean)	Source
Diarrhoea grade 1/2			
Neratinib without prophylaxis	55.1%	17.4	Puma data on file (2019)[81]
Neratinib with prophylaxis	47.5%	5.1	
Placebo	32.4%	6.5	
Diarrhoea grade 3/4			
Neratinib without prophylaxis	39.4%	2.7	Puma data on file (2019)[81]
Neratinib with prophylaxis	30.7%	1.6	
Placebo	1.1%	1.3	

Frequency of non-diarrhoea AEs for neratinib and placebo was taken from ExteNET and is presented in Table 38.

Table 38. ExteNET: grade 3 or 4 adverse event frequency in HR+ population ≤ 1 year from prior adjuvant trastuzumab

Adverse event	Incidence		Events (mean)		
	Neratinib	Placebo	Neratinib	Placebo	Source
Vomiting	3.6%	0.3%	1.50	1.0	Puma data on file (2018)[118]
Nausea	1.4%	0.3%	1.00	1.0	Puma data on file (2018)[118]
Abdominal pain	1.7%	0.2%	1.09	1.0	Puma data on file (2018)[118]
Fatigue	2.0%	0.3%	1.15	1.5	Puma data on file (2018)[118]
Alanine aminotransferase increased	1.2%	0.3%	1.00	1.0	Puma data on file (2018)[118]

Adverse event data used in the model analysis were taken directly from ExteNET. Given the timing of TEAEs reported in ExteNET and the short duration of these events, TEAEs were captured in the first cycle of the model in the base-case analysis. Disutility associated with AEs will have been captured in the HRQoL data collected in the trial used for the disease-free health state, so applying a disutility could double count the effect of the TEAEs. However, it is likely that trial-derived utility data will underestimate the disutility associated with TEAEs; therefore, applying a disutility to the trial-derived data will be reasonable and overestimate the effect of TEAEs and reflect a conservative assumption. Given the minor effect of AEs in the model and the negligible difference between treatment arms, no significant effect is expected on the results of the cost-effectiveness analysis.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

HRQoL data for the disease-free health state were collected in ExteNET using the EQ-5D-3L preference-based health-state utility questionnaire (EQ-5D Utility Index) at baseline and months 1, 3, 6, 9, and 12 (end of treatment)[51,53,54] (see Section B.2.6.1.4). Utility scores were based on a UK value set.[117] It was assumed that patients in remission following local recurrence data would have the same utility value based on clinical opinion and in line with previous NICE submissions. The utility values for the remaining health states were identified through an SLR (see Appendix M) and desktop searches of previous NICE submissions in similar indications to identify values relevant to the decision problem.

In accordance with the NICE reference case, utility estimates for the disease-free (iDFS) health state were derived from the EQ-5D-3L data collected in the ExteNET study. Values for local (non-metastatic) recurrence, remission (following local recurrence), and distant (metastatic) recurrence were based on assumptions and values obtained from the SLR or previous NICE appraisals in similar indications. The rationale for the selection of the values used in the analysis is explained in full below.

The indicated population at the time of entering the trial (and model analysis) is all disease free and therefore generalisable between arms. Given that there was no statistically significant difference between arms, the data were pooled to derive the disease-free health-state utility estimate (see Section B.3.4.1 for further details).

Data were available for only a small number of patients with a recurrence (11 patients had utility data after recurrence); as a result, no trial-derived EQ-5D data were available to derive estimates for the local and distant recurrence health states. In the base case, utility in the remission state was assumed equal to ‘disease free,’ as these health states are generalisable because the patients are disease free in

both. A similar assumption has been made in the pertuzumab appraisal (ID1192) for adjuvant treatment of early HER2+ breast cancer and in a neoadjuvant setting (TA424).[99]

Owing to utility data for both local and distant recurrence not being available from the ExteNET study, these values were obtained from the literature: Lidgren et al. (2007)[102] for local recurrence and Lloyd et al. (2006)[101] for distant recurrence. Both publications are well-established sources of utility data that have be used in previous NICE technology appraisals, including TA424 and ID1192.[99]

Lidgren et al. (2007)[102] reported results from a study of 361 patients with consecutive breast cancer attending the breast cancer outpatient clinic in Sweden. A direct time trade-off question was used to derive estimates for a range of breast cancer health states.

Lloyd et al. (2006)[101] reported results for 100 general public participants in the UK, using standard gamble to determine utility values for a range of health states.

The health-state utility values used in the base-case analysis and scenario analysis are reported in Table 39. The values selected for use in the base case use the trial data and the other published sources that were determined to be the most appropriate for the health state. In the scenario analysis, a single source Lidgren et al. (2007)[102] is used to provide consistency across all health states, removing potential effects of mixing data sources.

Table 39. Health-state utility values base case and scenario analysis

Health state	Health-state utility value (SE)	95% CI	Source
Health-state utility values: base case			
Disease free	0.837 (0.084)	0.829-0.846	ExteNET
Local recurrence	0.696 (0.070)	0.63-0.75	Lidgren et al. (2007)[102]
Remission (assumed equal to disease free)	0.837 (0.084)	0.829-0.846	ExteNET
Distant recurrence < 12 months	0.521 (0.052)	N/A	Lloyd et al. (2006)[101]
Distant recurrence > 12 months	0.521 (0.052)	N/A	Lloyd et al. (2006)[101]
Health-state utility values: scenario analysis			
Disease free	0.779 (0.078)	0.75-0.81	Lidgren et al. (2007)[102]
Local recurrence	0.696 (0.070)	0.63-0.75	Lidgren et al. (2007)[102]
Remission (assumed equal to disease free)	0.779 (0.078)	0.75-0.81	Lidgren et al. (2007)[102]

Health state	Health-state utility value (SE)	95% CI	Source
Distant recurrence < 12 months	0.685 (0.069)	0.62-0.735	Lidgren et al. (2007)[102]
Distant recurrence > 12 months	0.685 (0.069)	0.62-0.735	Lidgren et al. (2007)[102]

Abbreviations: CI, confidence interval; SE, standard error.

The effect of AEs is captured through the application of utility decrement over a stated time period based on trial data from ExteNET. In the case of diarrhoea, the effect of prophylaxis with loperamide is based on data from the CONTROL study. The selection of utility decrement values is based on selecting values available in literature that have been used in prior NICE appraisals. Grade 1 and 2 diarrhoea is rarely reported in NICE appraisals, and a value for this was obtained from published literature. Table 40 presents the utility decrements associated with AEs.

Table 40. Adverse event utility decrements and mean duration

Adverse event	Utility decrement	Duration of impact (weeks)		Source (Decrement; Duration)
		Neratinib	Placebo	
Diarrhoea grade 1/2	0.060	14.6 without prophylaxis 9.9 with prophylaxis	0.9	Beusterien et al. (2009)[119]; Puma data on file (2018)[120]; Puma data on file (2018)[121]
Diarrhoea grade 3/4	0.103	1.2 without prophylaxis 0.7 with prophylaxis	0.7	Lloyd et al. (2006)[101]; Puma data on file (2018)[120]; Puma data on file (2018)[121]
Vomiting	0.048	0.56	4.57	Nafees et al. (2008)[122];Puma data on file (2018)[118]
Nausea	0.048	1.13	4.29	Nafees et al. (2008)[122]; Puma data on file (2018)[118]
Abdominal pain	0.048	1.83	0.14	Assumption (same as nausea and vomiting); Puma data on file (2018)[118]
Fatigue	0.115	1.26	9.43	Lloyd et al. (2006)[101]; Puma data on file (2018)[118]
Alanine aminotransferase increased	0.048	1.2	9.64	Assumption (same as nausea and vomiting); Puma data on file (2018)[118]

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The types of costs considered in the economic model included drug costs related to the intervention (see Table 41), monitoring and management of the disease (see

Table 47 through Table 48), management of AEs (see Table 49), and costs associated with subsequent therapy (see Table 50 through Table 51).

An SLR was conducted to identify costs and resource use in the treatment and ongoing management of patients with adult patients with HR+/HER2+ breast cancer and who have completed a course of trastuzumab-based therapy within 1 year as described in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

The drug acquisition costs per treatment are presented below, with the unit costs for supportive treatment taken from the Electronic Market Information Tool (eMIT).

B.3.5.1.1 Neratinib

Per the anticipated licence, the model uses a dose of 240 mg neratinib, administered orally as 6 × 40 mg tablets taken once daily and continually for 1 year. The list price of a 180-tablet pack of neratinib is £4,500. Based on the list price, the total cost per patient per 240 mg dose is £150.

Although neratinib per the label should be given continually for 1 year, the actual mean treatment duration observed in ExteNET was [redacted] months when treatment discontinuation was accounted for. Thus, the treatment duration in the model was set to [redacted] months.[123]

In line with earlier NICE appraisals such as TA483, TA484, and ID923,[124-126] the model included the proportion of planned doses actually received to more accurately account for the real cost of therapy. This proportion was based on the relative actual dose intensity from ExteNET. The relative actual dose intensity is the ratio between actual dose intensity (the actual cumulative dose divided by the treatment duration) and the prescribed dose (240 mg). This showed that patients on treatment on average received [redacted] of the planned doses.[127]

B.3.5.1.2 Loperamide

Unit costs for loperamide were taken from the eMIT database. In the CONTROL study, two treatment protocols were used for loperamide prophylaxis; both were received for a period of 1 to 2 cycles (28-56 days), and the cost-effectiveness analysis assumes the maximum duration as a conservative assumption. The original protocol for prophylaxis treatment was for a 4 mg initial dose, then 2 mg every 4 hours on days 1-3 (i.e., 12 mg/day), then every 6 to 8 hours on days 4-56 (i.e., 6-8 mg/day) giving a total dose of 404 mg.[50] Later in the study, an amended protocol was used, with a 4 mg initial dose, then 4 mg three times per day on days 1-14 (i.e., 12 mg/day), then 4 mg twice per day on days 15-56 (i.e., 8 mg/day)

giving a total dose of 500 mg.[50] In the cost-effectiveness analysis, the amended protocol was used because it carried the higher cost (£2.50) and therefore was the conservative option.

Table 41 presents drug unit costs.

Table 41. Drug unit costs for loperamide

Treatment	Strength (mg)	Pack size	Cost per pack (£)	Cost per dose (£)	Source
Loperamide (OTC pack)	2	30	0.70	0.01	Department of Health (2018)[128]
Loperamide (standard pack)	2	10	0.10	0.01	Department of Health (2018)[128]
Loperamide (standard pack)	2	30	0.48	0.01	Department of Health (2018)[128]

Abbreviation: OTC, over the counter.

B.3.5.2 Health-state unit costs and resource use

There is limited published literature that explores in detail the resource use associated with adults with early-stage HR+, HER2-overexpressed/amplified breast cancer. The source used for resource utilisation per health state is the resource use previously assessed by NICE in the pertuzumab appraisal (ID1192) for adjuvant treatment of early HER2+ breast cancer assessment.

B.3.5.2.1 Health-state resource use

The model includes five health states: disease free, remission, local recurrence, distant recurrence, and dead. Health-state resource use and costs by health state are presented in Table 42 through Table 46.

Table 42. Health-state resource use and cost by health state: disease free

Resource use	Unit cost	% of patients	Resource use frequency		Source
			Year 1-4	Year > 4	
GP visit	£37.40	100	1	1	NICE (2018)[94]
Mammogram	£57.84	100	1	0	NICE (2018)[94]
Cost per 4-week cycle			£7.94	£3.12	

Abbreviation: GP, general practitioner.

Adapted from NICE (2018)[94] adjusting for a later initiation of treatment with neratinib.

Table 43. Health-state resource use and cost by health state: remission

Resource use	Unit cost	% of patients	Resource use frequency			Source
			Year 1	Years 2-5	Year > 5	
Oncologist visit	£140.87	100	2	0	0	NICE (2018)[94]
GP visit	£37.40	100	0	1	1	NICE (2018)[94]
Mammogram	£57.84	100	1	1	0	NICE (2018)[94]
ECHO scan	£97.18	70	4	0	0	NICE (2018)[94]
MUGA scan	£252.64	30	4	0	0	NICE (2018)[94]
Cost per 4-week cycle			£76.24	£7.94	£3.12	

Abbreviations: ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition.

Table 44. Health-state resource use and cost by health state: local recurrence

Resource use	Unit cost	% of patients	Resource use frequency	Source
			Per annum	
Oncologist visit	£140.87	100	2	NICE (2018)[94]
Mammogram	£57.84	100	1	NICE (2018)[94]
ECHO scan	£97.18	70	4	NICE (2018)[94]
MUGA scan	£252.64	30	4	NICE (2018)[94]

Resource use	Unit cost	% of patients	Resource use frequency Per annum	Source
CT scan	£109.81	75	2	NICE (2018)[94]
Cost per 4-week cycle			£89.96	

Abbreviations: CT, computed tomography; ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition.

Table 45. Health-state resource use and cost by health state: distant recurrence, first line

Resource use	Unit cost	% of patients	Resource use frequency Per annum	Source
GP visit	£37.40	100	12	NICE (2018)[94]
ECHO scan	£97.18	70	2	NICE (2018)[94]
MUGA scan	£252.64	30	2	NICE (2018)[94]
Clinical nurse (specialist)	£77.98	100	12	NICE (2018)[94]
District nurse (home visit)	£38.45	100	22	NICE (2018)[94]
CT scan	£109.81	75	One off	NICE (2018)[94]
Social worker	£84.00	100	One off	NICE (2018)[94]
Cost per 4-week cycle			£209.85	

Abbreviations: CT, computed tomography; ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition.

Table 46. Health-state resource use and cost by health state: distant recurrence, second line

Resource use	Unit cost	% of patients	Resource use frequency Per annum	Source
GP visit	£37.40	100	12	NICE (2018)[94]
Clinical nurse (specialist)	£77.98	100	12	NICE (2018)[94]
District nurse (home visit)	£38.45	100	24	NICE (2018)[94]
Cost per 4-week cycle			£192.28	

Abbreviation: GP, general practitioner.

Table 47 presents unit costs of resource use items included in the health-state costs.

Table 47. Monitoring costs

Resource	Cost per event	Source/notes
GP visit	£37.40	Section 10.3 page 127 Curtis and Burns (2018)[129]
Oncologist visit	£140.87	Clinical Oncology NHS Improvement (2018)[130]
Clinical nurse (specialist)	£77.89	Specialist nursing, breast care nursing/liaison, adult, face to face, N09AF NHS Improvement (2018)[130]
District nurse (home visit)	£38.45	District nurse, adult, face to face, N02AF NHS Improvement (2018)[130]
Social worker	£84.00	Section 11.1 page 139 Curtis and Burns (2018)[129]
Mammogram	£57.84	NICE (2017)[131]
ECHO scan	£97.18	Simple ECHO, aged ≥ 19 years, RD51A NHS Improvement (2018)[130]
CT scan	£109.81	CT scan of 3 areas, without contrast, RD25Z NHS Improvement (2018)[130]
MUGA scan	£252.64	CT scan of 1 area, with pre- and post-contrast, RN22Z NHS Improvement (2018)[130]

Abbreviations: CT, computed tomography; ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition.

An expert panel of clinicians suggested that additional follow-up would be required for patients on neratinib treatment. The SmPC states that liver function should be monitored at 1 week, then monthly for the first 3 months and every 6 weeks thereafter while on treatment; the frequency of liver function test in the analysis is calculated on this basis (Table 48).

Table 48. Additional monitoring frequency for neratinib patients

Resource	Frequency	Duration (years)	Source/notes
GP visit	11	1	Puma data on file (2017)[132]
Liver function test	10	1	NERLYNX® SmPC (2018)[1]

Abbreviation: GP, general practitioner;

B.3.5.3 Adverse reaction unit costs and resource use

Differences in the rates of grade ≥ 3/4 AEs between treatment arms were observed in the trial data, and those AEs occurring in ≥ 1.0% of all neratinib patients were included in the analysis. Table 49 presents AE unit costs. Adverse event costs for each treatment arm were calculated as the sum product of the cost of each AE and the proportion of AEs observed in the trial, resulting in an average cost per patient that in turn is applied to the modelled population.

Costs detailed in Table 49 are multiplied by AE frequencies detailed in Table 37 and Table 38.

Table 49. Adverse event costs

Adverse event	Cost per event	Source/notes
Diarrhoea grade 1/2[a]	£284.50	NHS Improvement (2018)[130], currency selection based on NICE (2015)[133]
Diarrhoea grade 3/4[a]	£2,072.15	
Vomiting[a]	£733.08	NHS Improvement (2018)[130], currency selection based on NICE (2017)[134]
Nausea[a]	£733.08	NHS Improvement (2018)[130], currency selection based on NICE (2017)[134]
Abdominal pain	£1,437.60	NHS Improvement (2018)[130]
Fatigue	£3,000.39	NHS Improvement (2018)[130]

[a] Inflated using Curtis and Burns (2018)[129].

B.3.6 Subsequent treatment costs following recurrence

Drug costs used in subsequent lines of treatment are taken from the eMIT and the British National Formulary (Table 50). The subsequent treatments were included to be aligned with the ongoing NICE appraisal of pertuzumab (ID1192)[94]. The data used in that submission were deemed representative for the UK by the ERG to that appraisal. Further, patients were note followed in ExteNET with regards to type of subsequent treatment and this information on subsequent treatment given in the trial was not available.

Table 50. Subsequent treatment unit costs

Treatment	Strength (mg)	Pack size	Cost per pack (£)	Source
Trastuzumab emtansine (Kadcyla)	100 mg	1 Vial	£1,641.01	MedicinesComplete (2019)[135]
	160 mg	1 Vial	£2,625.62	MedicinesComplete (2019)[135]
Trastuzumab IV (Herceptin)	150 mg	1 Vial	£366.66	MedicinesComplete (2019)[135]
Trastuzumab SC (Herceptin)	600 mg	1 Vial	£1,222.20	MedicinesComplete (2019)[135]
Pertuzumab IV (Perjeta)	420 mg/14 ml	1 Vial	£2,395.00	MedicinesComplete (2019)[135]
Capecitabine	500 mg	120 Tablets	£21.76	Department of Health (2018)[128]
Docetaxel	20 mg/1 ml	1 Vial	£3.85	Department of Health (2018)[128]

Abbreviations: BNF, British National Formulary; IV, intravenous; SC, subcutaneous.

Body surface area (1.80 m^2) and weight (72.64 kg) used to estimate the dose needed of each subsequent treatment were taken from the ExteNET population.[127]

Administration costs associated with subsequent therapy were taken from the NHS Reference Costs and are detailed in Table 51.

Table 51. Subsequent treatment administration costs

Currency description	Currency code	Cost	Source
Deliver more complex parenteral chemotherapy at first attendance	SB13Z	£309.22	NHS Improvement (2018)[130]
Deliver simple parenteral chemotherapy at first attendance	SB12Z	£247.74	NHS Improvement (2018)[130]

The treatment shares used in the ongoing NICE appraisal of pertuzumab (ID1192)[94] were partially based on company internal forecasts made by Roche. Thus, it was not possible for Puma to assess the validity of those data. However, the proportion of each type of subsequent treatment used in ID1192 was well aligned with clinical opinion on treatment shares provided to Puma (see Appendix M). Therefore, for consistency and comparability, the treatment shares used in the ongoing NICE appraisal of pertuzumab (ID1192) have also been used in the current model. Table 52 shows the proportion of each type of subsequent treatment used in the model.

Table 52. Subsequent treatment following recurrence

Health state	Regimen	No. of cycles	Cost	Treatment share	Weighted cost	State cost
Non-metastatic recurrence	Trastuzumab IV + docetaxel	18	£25,573.50	50%	£12,786.75	£26,673.48
	Trastuzumab SC + docetaxel	18	£27,773.46	50%	£13,886.73	
First-line early metastatic breast cancer	Trastuzumab IV + docetaxel	23.7	£33,535.48	23%	£7,679.63	£111,973.06
	Pertuzumab + trastuzumab + docetaxel	37.4	£146,308.58	71%	£104,171.71	
	Docetaxel	6	£2,063.22	6%	£121.73	
Second-line early metastatic breast cancer	Trastuzumab IV and capecitabine	9.4	£13,510.90	6%	£767.66	£70,463.19
	Trastuzumab emtansine	19.3	£88,049.11	76%	£67,037.39	
	Lapatinib and capecitabine	12.3	£14,542.41	6%	£826.27	
	Trastuzumab SC and capecitabine	9.4	£14,654.88	13%	£1,831.86	

Abbreviations: IV, intravenous; SC, subcutaneous.

B.3.6.1 Miscellaneous unit costs and resource use

There were no additional costs included in the model except those outlined in the previous section.

B.3.6.2 Summary of base-case analysis inputs

Table 53 presents a summary of the key variables

Table 53. Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Age	51.18 years	Fixed	
Body surface area	1.80	SD: 0.22 Normal	Section B.3.6
Body weight	72.64 kg	SD: 16.67 Normal	Section B.3.6
Time horizon	55 years	Fixed	Section B.3.2.2
Discount rate: outcomes	3.5%	Fixed	Section B.3.2.2
Discount rate: costs	3.5%	Fixed	Section B.3.2.2
Clinical parameters			
Treatment duration	[redacted] months	[redacted]	Section B.3.5.1.1
% Local recurrence: placebo	31%	Beta (28, 63)	Section B.3.3.3
% Local recurrence: neratinib	18%	Beta (9, 40)	Section B.3.3.3
Dose intensity	[redacted]		Section B.3.5.1.1
Survival model: iDFS	ExteNET: flexible-spline Weibull 1 knot General population mortality: flexible-spline Weibull 2 knot	Multivariate normal	Section B.3.3.1
Survival model: PDRS	Gompertz	Multivariate normal	Section B.3.3.5.1
Adverse event: incidence of diarrhoea and grade ≥ 3 adverse events			
Diarrhoea grade 1/2: neratinib without prophylaxis	55.1%	SE: 5.5% Normal	Section B.3.4.4, Table 37
Diarrhoea grade 1/2: neratinib with prophylaxis	47.5%	SE: 4.8% Normal	Section B.3.4.4, Table 37
Diarrhoea grade 1/2: placebo	32.4%	SE: 3.2% Normal	Section B.3.4.4, Table 37
Diarrhoea grade 3/4: neratinib without prophylaxis	39.4%	SE: 3.9% Normal	Section B.3.4.4, Table 37

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Diarrhoea grade 3/4: neratinib with prophylaxis	30.7%	SE: 3.1% Normal	Section B.3.4.4, Table 37
Diarrhoea grade 3/4: placebo	1.1%	SE: 0.1% Normal	Section B.3.4.4, Table 37
Vomiting: neratinib	3.6%	Beta (24, 638)	Section B.3.4.4, Table 38
Nausea: neratinib	1.4%	Beta (9, 653)	Section B.3.4.4, Table 38
Abdominal pain: neratinib	1.7%	Beta (11, 651)	Section B.3.4.4, Table 38
Fatigue: neratinib	2.0%	Beta (13, 649)	Section B.3.4.4, Table 38
Alanine aminotransferase increased: neratinib	1.2%	Beta (8, 654)	Section B.3.4.4, Table 38
Vomiting: placebo	0.3%	Beta (2, 655)	Section B.3.4.4, Table 38
Nausea: placebo	0.3%	Beta (2, 655)	Section B.3.4.4, Table 38
Abdominal pain: placebo	0.2%	Beta (1, 656)	Section B.3.4.4, Table 38
Fatigue: placebo	0.3%	Beta (2, 655)	Section B.3.4.4, Table 38
Alanine aminotransferase increased: placebo	0.3%	Beta (2, 655)	Section B.3.4.4, Table 38
Adverse events: mean number of diarrhoea and grade ≥ 3 adverse events per patient with at least one event			
Diarrhoea grade 1/2: neratinib without prophylaxis	17.4	SE: 1.735 Normal	Section B.3.4.4, Table 37
Diarrhoea grade 1/2: neratinib with prophylaxis	5.1	SE: 0.507	Section B.3.4.4, Table 37
Diarrhoea grade 1/2: placebo	6.5	SE: 0.645	Section B.3.4.4, Table 37
Diarrhoea grade 3/4: neratinib without prophylaxis	2.7	SE: 0.273	Section B.3.4.4, Table 37
Diarrhoea grade 3/4: neratinib with prophylaxis	1.6	SE: 0.155	Section B.3.4.4, Table 37
Diarrhoea grade 3/4 - placebo	1.3	SE: 0.129	Section B.3.4.4, Table 37
Vomiting: neratinib	1.5	SE: 0.15 Gamma (100, 0.015)	Section B.3.4.4, Table 38

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Nausea: neratinib	1.0	SE: 0.1 Gamma (100, 0.01)	Section B.3.4.4, Table 38
Abdominal pain: neratinib	1.09	SE: 0.11 Gamma (100, 0.0109)	Section B.3.4.4, Table 38
Fatigue: neratinib	1.15	SE: 0.12 Gamma (100, 0.0115)	Section B.3.4.4, Table 38
Alanine aminotransferase increased: neratinib	1.0	SE: 0.1 Gamma (100, 0.01)	Section B.3.4.4, Table 38
Vomiting: placebo	1.0	SE: 0.1 Gamma (100, 0.01)	Section B.3.4.4, Table 38
Nausea: placebo	1.0	SE: 0.1 Gamma (100, 0.01)	Section B.3.4.4, Table 38
Abdominal pain: placebo	1.0	SE: 0.1 Gamma (100, 0.01)	Section B.3.4.4, Table 38
Fatigue: placebo	1.5	SE: 0.15 Gamma (100, 0.015)	Section B.3.4.4, Table 38
Alanine aminotransferase increased: placebo	1.0	SE: 0.1 Gamma (100, 0.01)	Section B.3.4.4, Table 38
Health-state utilities			
Disease free	0.837	SE: 0.084 Beta (15.463, 3.01)	Section B.3.4.5
Local recurrence	0.696	SE: 0.070 Beta (29.704, 12.97)	Section B.3.4.5
Remission (assumed equal to disease free)	0.837	SE: 0.84 Beta: (15,463, 3.01)	Section B.3.4.5
Distant recurrence < 12 months	0.521	SE: 0.052 Beta: (47.369, 43.53)	Section B.3.4.5
Distant recurrence > 12 months	0.521	SE: 0.052 Beta: (47.369, 43.53)	Section B.3.4.5
Adverse event utility decrements			
Diarrhoea grade 1/2	0.060	SE: 0.006 Beta: (93.94, 1,471.73)	Section B.3.4.5
Diarrhoea grade 3/4	0.103	SE: 0.103 Beta: (89.597, 780.28)	Section B.3.4.5
Vomiting	0.048	SE: 95.15 Beta: (95.15, 1,886.32)	Section B.3.4.5
Nausea	0.048	SE: 95.15 Beta: (95.15, 1,886.32)	Section B.3.4.5
Abdominal pain	0.048	SE: 95.15 Beta: (95.15, 1,886.32)	Section B.3.4.5
Fatigue	0.115	SE: 0.115 Beta: (88.385, 680.18)	Section B.3.4.5

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Alanine aminotransferase increased	0.048	SE: 95.15 Beta: (95.15, 1,886.32)	Section B.3.4.5
Treatment share local recurrence			
Trastuzumab IV + docetaxel	50%	SE: 0.05 Gamma (49.5, 49.5)	Section B.3.6 Table 52
Trastuzumab IV + docetaxel	50%	SE: 0.05 Gamma (49.5, 49.5)	Section B.3.6 Table 52
Treatment share first-line distant recurrence			
Trastuzumab IV + docetaxel	22.9%	SE: 0.02 Gamma (76.87, 258.81)	Section B.3.6 Table 52
Pertuzumab + trastuzumab + docetaxel	71.2%	SE: 0.02 Gamma (28.09, 11.36)	Section B.3.6 Table 52
Docetaxel	5.9%	SE: 0.01 Gamma (94.04, 1,499.87)	Section B.3.6 Table 52
Treatment share second-line distant recurrence			
Trastuzumab IV + capecitabine	5.7%	SE: 0.06 Gamma (94.26, 1,564.74)	Section B.3.6 Table 52
Trastuzumab emtansine	76.1%	SE: 0.08 Gamma (23.10, 7.24)	Section B.3.6 Table 52
Lapatinib + capecitabine	5.7%	SE: 0.01 Gamma (94.26, 1,564.74)	Section B.3.6 Table 52
Trastuzumab SC + capecitabine	12.5%	SE: 0.01 Gamma (87.38, 611.63)	Section B.3.6 Table 52
Technology acquisition costs (unit costs)			
Neratinib	£4,500	Fixed	Section B.3.5.1.1
Monitoring unit costs			
GP visit	£37.40	SD: 3.74 Gamma (28.05, 46.75)	Section B.3.5.2
Oncologist visit	£140.87	SD: 14.09 Gamma (105.66, 176.09)	Section B.3.5.2
Clinical nurse (specialist)	£77.89	SD: 7.80 Gamma (58.48, 97.47)	Section B.3.5.2
District nurse (home visit)	£38.45	SD: 3.85 Gamma (28.84, 48.07)	Section B.3.5.2
Social worker	£84.00	SD: 8.40 Gamma (63.00, 105.00)	Section B.3.5.2
Digital Mammogram	£57.84	SD: 5.78 Gamma (43.38, 72.30)	Section B.3.5.2

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
ECHO scan	£97.18	SD: 9.72 Gamma (87.46, 106.89)	Section B.3.5.2
CT scan	£109.81	SD: 10.98 Gamma (82.35, 137.26)	Section B.3.5.2
MUGA scan	£252.64	SD: 25.26 Gamma (227.38, 277.91)	Section B.3.5.2
Health-state costs per 4-week cycle			
Disease free, year 1-4	£7.94	SD: 0.79 Gamma (5.95, 9.92)	Section B.3.5.2
Disease free, year 4+	£3.12	SD: 0.312 Gamma (2.34, 3.90)	Section B.3.5.2
Remission, year 1	£76.24	SD: 7.62 Gamma (57.18, 95.30)	Section B.3.5.2
Remission, year 2-5	£7.94	SD: 0.79 Gamma (5.95, 9.92)	Section B.3.5.2
Remission, year 6+	£3.12	SD: 0.312 Gamma (2.34, 3.90)	Section B.3.5.2
Local recurrence, per annum	£89.96	SD: 8.99 Gamma (67.47, 112.45)	Section B.3.5.2
Distant recurrence: first line	£209.85	SD: 20.9 Gamma (188.86, 230.83)	Section B.3.5.2
Distant recurrence: second line	£192.28	SD: 19.23 Gamma (173.06, 211.51)	Section B.3.5.2
Adverse event unit costs			
Diarrhoea grade 1/2	£284.50	SD: 28.45 Gamma (100, 2.85)	Section B.3.5.3
Diarrhoea grade 3/4	£2,072.15	SD: 207.21 Gamma (100, 20.72)	Section B.3.5.3
Vomiting	£733.08	SD: 73.31 Gamma (100, 7.33)	Section B.3.5.3
Nausea	£733.08	SD: 73.31 Gamma (100, 7.33)	Section B.3.5.3
Abdominal pain	£1,437.60	SD: 143.76 Gamma (100, 14.38)	Section B.3.5.3
Fatigue	£3,000.39	SD: 300.03 Gamma (100, 30.00)	Section B.3.5.3
Alanine aminotransferase increased	£627.42	SD: 62.74 Gamma (100, 6.27)	Section B.3.5.3
Subsequent therapy cost			

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Trastuzumab emtansine (Kadcyla)	£1,641.01	Fixed	Section B.3.6
Trastuzumab emtansine (Kadcyla)	£2,625.62	Fixed	Section B.3.6
Trastuzumab IV (Herceptin)	£366.66	Fixed	Section B.3.6
Trastuzumab SC (Herceptin)	£1,222.20	Fixed	Section B.3.6
Pertuzumab IV (Perjeta)	£2,395.00	Fixed	Section B.3.6
Capecitabine	£21.76	Fixed	Section B.3.6
Docetaxel	£3.85	Fixed	Section B.3.6

Abbreviations: CT, computed tomography; ECHO, echocardiogram; GP, general practitioner; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IV, intravenous; MUGA, multigated acquisition; SC, subcutaneous; SD, standard deviation; SE, standard error.

B.3.6.3 Assumptions

Table 54. Key assumptions in the economic model

Parameter	Base-case assumption	Justification
Survival model: iDFS	ExteNET: flexible-spline Weibull 1 knot General population mortality: flexible-spline Weibull 2 knot	Choice of extrapolation model was based on statistical goodness of fit, visual fit, clinical plausibility, and validation with external evidence.
Survival model: PDRS	Gompertz	Choice of extrapolation model was based on statistical goodness of fit and visual fit.
HRQoL	Based on EQ-5D data collected in ExteNET and published literature. Utility values were allocated by health state and not differentiated by treatment arm.	Consistent with NICE recommendations.
Duration of treatment effect	Treatment effect was continued while patients were at increased risk of iDFS event compared with general population.	In the clinical trial, a treatment effect was maintained 4 years after treatment; extrapolations did not indicate that it would be likely for the treatment effect to disappear within the model time horizon.
Cancer-related mortality	Cancer-related mortality was only applied from distant recurrence. Mortality from all other health states was based on general population mortality.	This is in line with previous NICE appraisals, and data from ExteNET confirmed that few patients died without a distant recurrence.
Proportion of local and distant recurrence between arms	Proportion of local and distant recurrence was modelled specifically per treatment arm.	Data from ExteNET showed a small difference in site of recurrence between arms.

Parameter	Base-case assumption	Justification
Time in local recurrence	Patients stayed in the local recurrence state for 12 months before being able to transition to remission.	This approach follows previous NICE assessments in which the assumption was agreed to be reasonable.

Abbreviations: HRQoL, health-related quality of life; iDFS, invasive disease-free survival; PDRS, postdistant recurrence survival.

B.3.7 Base-case results

The results of the model with base-case assumptions are presented below.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Table 55 presents total costs, LYGs, QALYs, and incremental costs per QALY for neratinib compared with placebo. Compared with placebo, neratinib generated 0.80 incremental QALYs and 0.88 incremental LYGs, and the neratinib-treated cohort had higher total lifetime costs. The incremental cost-effectiveness ratio (ICER) was £24,585 per QALY gained.

Table 55. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Placebo	[redacted]	17.00	14.03				
Neratinib	[redacted]	17.88	14.83	[redacted]	0.88	0.80	24,585

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality-adjusted life-year.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A second-order Monte Carlo simulation was run for 5,000 iterations. Results of the probabilistic sensitivity analysis are shown in Table 56, which also shows results from the deterministic analysis for comparison. The probabilistic ICER was £24,413 per QALY gained compared with £24,585 per QALY gained in the deterministic analysis.

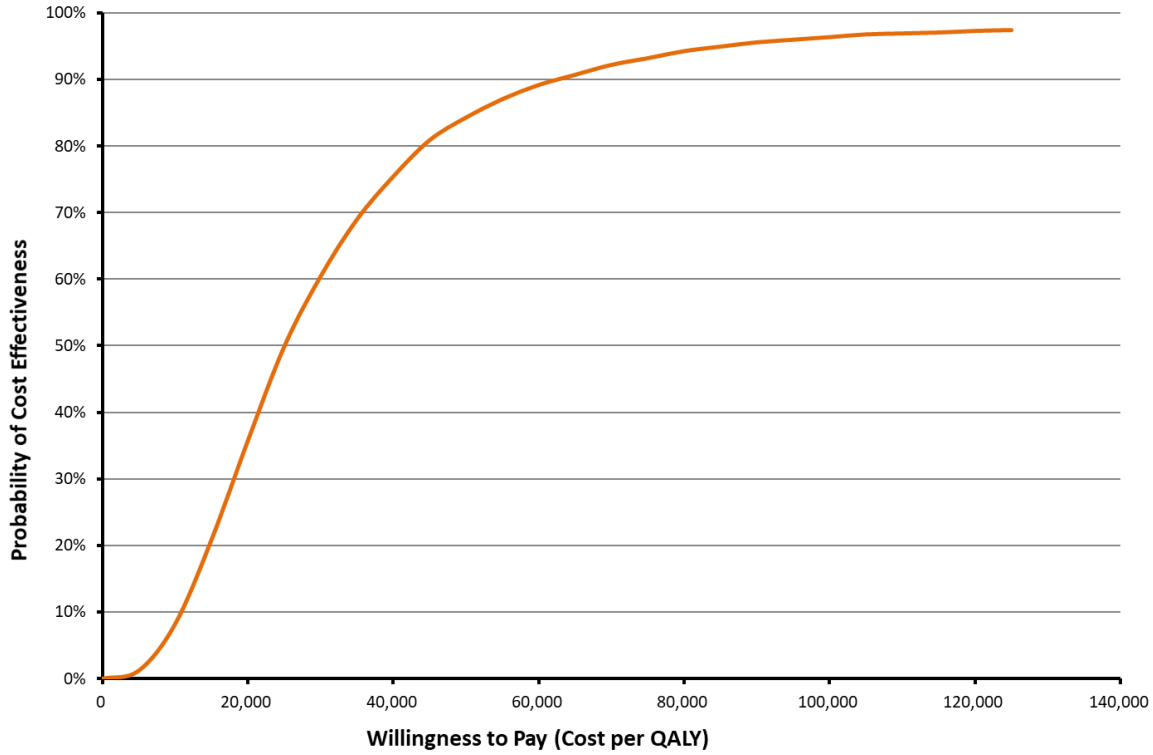
Table 56. Results of the probabilistic sensitivity analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Deterministic results					
Placebo	[redacted]	14.03			
Neratinib	[redacted]	14.83	[redacted]	0.80	24,585
Probabilistic results					
Placebo	[redacted]	13.99			
Neratinib	[redacted]	14.79	[redacted]	0.80	24,413

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Figure 39 presents the cost-effectiveness acceptability curve. The cost-effectiveness acceptability curve shows that neratinib has a 36% and 60% probability of being cost-effective compared with placebo at a willingness-to-pay threshold of £20,000 and £30,000 per QALY, respectively.

Figure 39. Cost-effectiveness acceptability curve



Abbreviation: QALY, quality-adjusted life-year.

Figure 40 presents the cost-effectiveness plane, which shows that most of the 5,000 iterations ended up in the NE quadrant. This means that neratinib resulted in more QALYs and higher costs compared with placebo.

Figure 40. Cost-effectiveness plane

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

B.3.8.2 Deterministic sensitivity analysis

Table 57 summarises the deterministic sensitivity analyses. It is evident from Table 57 and Figure 41 that, across most scenarios tested, the ICER for neratinib does not change significantly. The largest impact on the ICER is driven by utility in the iDFS health state (due to the considerably longer time in this health state in the neratinib arm) and the duration of therapy for neratinib.

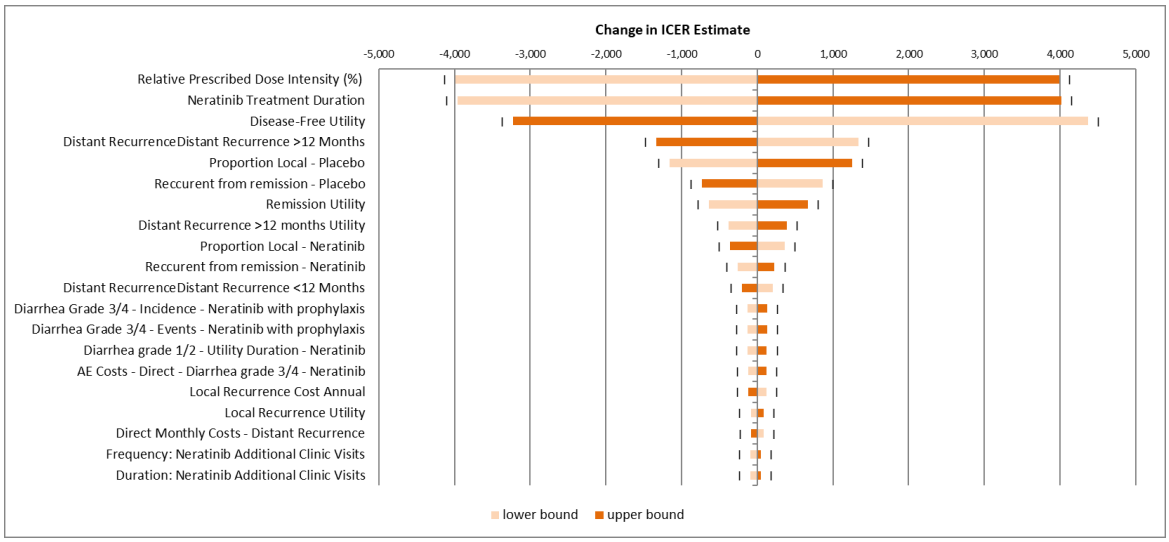
Table 57. Deterministic sensitivity analysis

Parameter	Base-case value	Analysis	Values for DSA	Incremental cost per QALY (£)
Base-case analysis				
Relative prescribed dose intensity (%)	[redacted]	Lower	[redacted]	[redacted]
		Higher	[redacted]	[redacted]
Neratinib treatment duration	[redacted]	Lower	[redacted]	[redacted]
		Higher	[redacted]	[redacted]
Disease-free	0.84	Lower	0.75	28,954
		Higher	0.92	21,361
	175,390	Lower	157,851	25,918

Parameter	Base-case value	Analysis	Values for DSA	Incremental cost per QALY (£)
Distant recurrence distant recurrence >12 months		Higher	192,929	23,251
Proportion local -placebo	0.31	Lower	0.28	23,429
		Higher	0.34	25,835
Recurrent from remission - placebo	0.0076	Lower	0.0068	25,448
		Higher	0.0083	23,852
Remission	0.84	Lower	0.75	23,949
		Higher	0.92	25,255
Distant recurrence >12 months	0.52	Lower	0.47	24,209
		Higher	0.57	24,972
Proportion local - neratinib	0.18	Lower	0.17	24,950
		Higher	0.20	24,228
Recurrent from remission - neratinib	0.0076	Lower	0.007	24,330
		Higher	0.008	24,813
Distant recurrence distant recurrence <12 months	175,390	Lower	157,851	24,787
		Higher	192,929	24,382
Diarrhea grade 3/4 - incidence - neratinib with prophylaxis	0.31	Lower	0.28	24,458
		Higher	0.34	24,712
Diarrhea grade 3/4 - events - neratinib with prophylaxis	1.55	Lower	1.40	24,458
		Higher	1.71	24,712
AE costs - direct - diarrhea grade 3/4 - neratinib	15	Lower	13	24,460
		Higher	16	24,711
Local recurrence cost annual	2072	Lower	1,865	24,465
		Higher	2,279	24,705

Abbreviations: AE, adverse event; DSA, deterministic sensitivity analysis; QALY, quality-adjusted life-year.

Figure 41. Ex tornado diagram for DSA of neratinib vs placebo showing impact on the ICER



Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio.

Note: The quadrant where the ICER falls is shown in the figure: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates).

B.3.8.3 Scenario analysis

Scenario analyses were undertaken to investigate the effect of certain model inputs on costs and outcomes. All undertaken scenario analyses are presented in Table 58, as shown, waning of treatment effect had the largest impact on the ICER. For all other scenarios the impact on the ICER were marginal.

Table 58. Scenario analyses

Scenario	Alternative input	Base-case value	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case				[redacted]	0.80	24,585
1	Second-best-fitting distribution for ExteNET iDFS	Flexible-spline Weibull 1 knot	Gompertz	[redacted]	0.70	30,190
2	Second-best-fitting distribution for general population mortality	Flexible-spline Weibull 2 knot	Gompertz	[redacted]	0.80	24,793
3	Including HERA data in the extrapolation of iDFS	Using ExteNET and general	Using ExteNET, HERA, and general	[redacted]	0.80	24,912

Scenario	Alternative input	Base-case value	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
		population mortality	population mortality			
4	Second-best-fitting distribution used for PDRS	Gompertz	Exponential	[redacted]	0.76	26,285
5	Waning of treatment effect	No treatment effect waning except for earlier crossover to general population mortality for neratinib arm	Waning to no treatment effect at 13.9 years from randomisation	[redacted]	0.70	31,677
6	Not stratifying PDRS by time of distant recurrence; < 12 months and ≥ 12 months	Separate survival incorporated for distant recurrence; < 12 months and ≥ 12 months	Same survival assumed regardless of time of distant recurrence	[redacted]	0.80	25,286
7	Proportion of local and distant recurrence	Treatment arm–specific proportion of local and distant recurrence	Average proportion of local and distant recurrence across both treatment arms	[redacted]	0.89	22,022
8	Time in local recurrence before transitioning to remission	12 months	6 months	[redacted]	0.80	25,063

Abbreviations: HERA, HERceptin Adjuvant trial; iDFS, invasive disease-free survival; PDRS, postdistant recurrence survival; QALY, quality-adjusted life-year.

B.3.8.4 Summary of sensitivity analyses results

As shown in Section B.3.8, the results of the sensitivity analyses are robust and not sensitive to changes in important parameters. The scenario analyses show that the presented base-case ICER is conservative in relation to most parameters.

B.3.9 Subgroup analysis

No subgroup analyses were performed

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

ExteNET is the longest available data set for patients treated with neratinib; thus, external validation of the intervention arm for the extrapolations has not been possible. However, for the placebo arm, there are (as noted in Section B.3.3.1 and Appendix L) relevant data for comparison available with longer-term follow-up. The current analysis submission has also explored multiple options of incorporating external evidence to aid the prediction of long-term survival as outlined in Section B.3.3.1. As shown in that section, the extrapolated curves from ExteNET were very well aligned with an approach incorporating external data from the HERA trial. Thus, this provides confidence that the extrapolations of results from the ExteNET are reasonable.

B.3.10.1.1 External expert validation

Throughout the development of the economic model and submission, clinical and economic expert advice was sought to ensure both clinical and economic validity.

- An early advisory board meeting was held on 10 April 2017 via teleconference. A UK health economist who had actively participated in previous NICE technology appraisals in oncology and two UK clinical oncologists were included in the discussions.
- A UK advisory workshop was held on 13 November 2018 and attended by two UK health economists with expertise in UK HTAs.
- A one-on-one phone interview was conducted on 20 December 2018 with one UK clinical expert who was selected based on his knowledge of UK clinical practice in treating patients with breast cancer.

The discussions during the advisory boards and subsequent interviews focused on the following:

- Model structure
- Comparator and subsequent treatments
- Validation of resource use and costs included in the economic model
- Modelling of OS
- Modelling of iDFS and duration of treatment effect

B.3.11 Interpretation and conclusions of economic evidence

Consistency of the results from the economic evaluation with the published economic literature

This is, to our knowledge, the first economic evaluation undertaken for neratinib in the extended adjuvant treatment of adult patients with early-stage HR+, HER2-overexpressed/amplified breast cancer and who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy. Therefore, there are no published economic analyses with which to compare.

Generalisability of the results to clinical practice in England and relevance to all patients as identified in the decision problem

The analysis is likely to be directly applicable to clinical practice in England as follows:

- The ExteNET trial included 13 UK study sites and the patient population in ExteNET and the economic analysis are likely to be reflective of patients with early and locally advanced breast cancer in the UK in terms of baseline characteristics and the treatment pathway in early breast cancer. Therefore, the clinical outcomes are likely to be applicable to the patient population in England.
- UK clinical experts confirmed that the prophylactic regimens for diarrhoea that were assessed in the CONTROL trial are in line with UK clinical practice.
- The economic model structure is in line with other oncology models and previous breast cancer submissions to NICE.[94]
- The resource use and costs in the analysis have been validated by UK clinicians and were sourced from UK-based publications (e.g., NHS Reference Costs and British National Formulary) and previous NICE technology appraisals.[94,130,136]

Strengths and weaknesses of the evaluation

The economic model is based on patient-level data from ExteNET with 5 years of follow-up, including initial treatment pattern, QoL, and iDFS for both neratinib and placebo. Although this is a long follow-up, additional survival extrapolations were essential to estimate iDFS and OS within the model time horizon. Extensive work has been undertaken to investigate possible options of including a combination of trial data and external evidence to ensure these extrapolations are as robust as possible. The alternative methods and data sets used in the survival extrapolations resulted in highly consistent predictions, strengthening the validity of the modelled data. Limitations in the form of OS data per treatment arm only becoming available

from [redacted] were overcome by using the blinded PDRS data from ExteNET, assuming equal PDRS for both arms. In terms of resource utilisation, inputs were validated and aligned with previous NICE technology appraisals and identified from UK sources. A limitation with the results of the current analyses is that the cost of all treatments is based on list prices. This is aligned with NICE's request during the decision problem meeting, but results are likely to be subject to change because of a potential discount available for treatments included.

Concluding the economic analyses

In the ExteNET trial, neratinib has shown a significant improvement in iDFS compared with placebo (hazard rate, 0.58; 95% CI, 0.41-0.82).

The economic analyses based on the clinical data from ExteNET predicted that patients with early HR+/HER2+ breast cancer within 1 year of trastuzumab therapy treatment with neratinib would gain 0.80 QALYs versus placebo. This resulted in an ICER of £24,585 per QALY based on the list price of all treatments included in the analysis.

B.4 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Neratinib for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab [ID981]

Company responses to clarification questions

March 2019

File name	Version	Contains confidential information	Date
ID981_neratinib_response to clarificationQs_March_12_2019_Redacted	1	NO	12 March 2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A1. Priority Question: Please provide full search strategies for all databases, conferences and trials registers listed in Appendix G. Currently only the MEDLINE strategies are provided.

All remaining search strategies for the original and updated searches in Embase, EconLit, Biosis, and the Cochrane Library are provided below.

Original Economic Systematic Review - Embase Literature Search Strategy (Conducted on 25 October, 2016)

Search No.	Search Terms	No. of Articles
Disease		
#1	'breast tumor'/exp OR (breast NEXT/1 neoplasm*):ti,ab,de OR (breast NEXT/1 cancer*):ti,ab,de OR (breast NEXT/1 carcinoma*):ti,ab,de OR (breast NEXT/1 tumor*):ti,ab,de OR (breast NEXT/1 tumour*):ti,ab,de OR (mammary NEXT/1 cancer*):ti,ab,de OR (mammary NEXT/1 carcinoma*):ti,ab,de OR (mammary NEXT/1 neoplasm*):ti,ab,de	396,665
Population		
#2	#1 AND (('epidermal growth factor receptor 2'/exp/mj OR 'erbB-2':ti,ab,de OR erbB2:ti,ab,de OR 'erbB 2':ti,ab,de OR 'human epidermal growth factor receptor 2':ti,ab,de OR (oncogene:ti,ab,de AND neu:ti,ab,de) OR HER2*:ti,ab,de OR 'HER-2':ti,ab,de OR 'HER 2':ti,ab,de) AND ('adjuvant chemoradiotherapy'/exp OR 'adjuvant chemotherapy'/exp OR 'adjuvant therapy'/exp OR adjuvant*:ti,ab,de OR neoadjuvant*:ti,ab,de OR (neo NEXT/1 adjuvant*):ti,ab,de))	9,301
Economic Models		
#3	#2 AND ('cost benefit analysis'/exp OR 'statistical model'/exp OR 'cost'/exp OR 'economics'/exp OR 'health economics'/exp OR 'pharmacoeconomics'/exp OR 'cost control'/exp OR (cost NEXT/1 effective*):ti,ab,de OR modeling:ti,ab,de OR modelling:ti,ab,de OR (economic NEXT/1 model*):ti,ab,de OR (model*:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de OR economic*:ti,ab,de OR pharmacoeconomic*:ti,ab,de)) OR Markov:ti,ab,de OR 'decision analysis':ti,ab,de OR	543

Search No.	Search Terms	No. of Articles
	'decision-analytic models':ti,ab,de OR 'cost consequence':ti,ab,de OR ((cost:ti,ab,de OR costs:ti,ab,de) AND (effective*:ti,ab,de OR utilit*:ti,ab,de OR benefit*:ti,ab,de OR minimi*:ti,ab,de)) OR 'discrete event simulation':ti,ab,de OR 'cost analysis':ti,ab,de OR 'cost-analysis':ti,ab,de OR 'cost-minimisation analysis':ti,ab,de OR (economic NEXT/1 benefit*):ti,ab,de OR 'cost utility':ti,ab,de OR 'cost-utility':ti,ab,de OR costminimization:ti,ab,de OR costminimisation:ti,ab,de OR 'cost-minimization':ti,ab,de OR 'cost-minimisation':ti,ab,de OR 'cost minimization':ti,ab,de OR 'cost minimisation':ti,ab,de OR 'budget impact':ti,ab,de OR econometric:ti,ab,de OR 'economic evaluation':ti,ab,de)	
Cost and Resource Use		
#4	#2 AND ('health care utilization'/exp OR 'fee'/exp OR 'health care cost'/exp OR 'cost of illness'/exp OR 'hospitalization'/exp OR 'length of stay'/exp OR 'drug utilization'/exp OR (('physician'/exp OR 'general practitioner'/exp OR 'emergency treatment'/exp OR 'emergency health service'/exp) AND ('health care utilization'/exp OR 'health economics'/exp)) OR 'absenteeism'/exp OR 'presenteeism'/exp OR 'medical leave'/exp OR 'return to work'/exp OR 'resource use':ti,ab,de OR 'resource utilization':ti,ab,de OR 'resource utilisation':ti,ab,de OR (resource NEXT/1 utili*):ti,ab,de OR 'health care use':ti,ab,de OR 'health service use':ti,ab,de OR 'health services use':ti,ab,de OR 'health care utilization':ti,ab,de OR 'healthcare utilization':ti,ab,de OR 'health care utilisation':ti,ab,de OR 'healthcare utilisation':ti,ab,de OR 'health resource utilization':ti,ab,de OR 'health resource utilisation':ti,ab,de OR 'health service utilization':ti,ab,de OR 'health service utilisation':ti,ab,de OR 'health services utilization':ti,ab,de OR 'health services utilisation':ti,ab,de OR (Economic*:ti AND burden*:ti) OR economic*:ti OR pharmacoeconomic*:ti,ab,de OR (pharmaco NEXT/1 economic*):ti,ab,de OR 'pharmaceutical economics':ti,ab,de OR price*:ti,ab,de OR pricing:ti,ab,de OR cost:ti,ab,de OR costs:ti,ab,de OR budget*:ti,ab,de OR expenditure*:ti,ab,de OR 'health care cost':ti,ab,de OR 'healthcare cost':ti,ab,de OR 'health care costs':ti,ab,de OR 'healthcare costs':ti,ab,de OR 'productivity cost':ti,ab,de OR 'productivity costs':ti,ab,de OR 'societal cost':ti,ab,de OR 'societal costs':ti,ab,de OR ((direct:ti,ab,de OR indirect:ti,ab,de) AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (medication:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (physician:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (hospitalization:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (hospitalisation:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR hospitalization:ti,ab,de OR hospitalisation:ti,ab,de OR 'hospital visit':ti,ab,de OR medication:ti,ab,de OR 'physician visit':ti,ab,de OR 'GP visit':ti,ab,de OR 'general practitioner visit':ti,ab,de OR 'ED visit':ti,ab,de OR 'emergency department visit':ti,ab,de OR 'emergency room visit':ti,ab,de OR 'ER visit':ti,ab,de OR employ*:ti OR unemploy*:ti OR absenteeism:ti,ab,de OR presenteeism:ti,ab,de OR ('missed work' NEXT/1 day*):ti,ab,de OR 'work absence':ti,ab,de OR 'sickness absence':ti,ab,de OR 'sick leave':ti,ab,de OR 'disability leave':ti,ab,de OR (sick NEXT/1 day*):ti,ab,de OR (illness NEXT/1 day*):ti,ab,de)	518
Utility		
#5	#2 AND ('quality of life'/exp OR 'quality adjusted life year'/exp OR 'health utility':ti,ab,de OR 'health utilities':ti,ab,de OR productivity:ti,ab,de OR EuroQol:ti,ab,de OR 'standard gamble':ti,ab,de OR 'time trade off':ti,ab,de OR 'time trade-off':ti,ab,de OR 'time tradeoff':ti,ab,de OR TTO:ti,ab,de OR EQ5D:ti,ab,de OR 'EQ-5D':ti,ab,de OR 'EQ 5D':ti,ab,de OR 'EuroQoL 5D':ti,ab,de OR EORTC:ti,ab,de OR 'health utility index':ti,ab,de OR 'health utilities index':ti,ab,de OR (health:ti,ab,de AND utilit*:ti,ab,de AND index:ti,ab,de) OR HUI:ti,ab,de OR 'SF-6D':ti,ab,de OR sf6*:ti,ab,de OR 'sf 6':ti,ab,de OR 'short form 6':ti,ab,de OR 'shortform 6':ti,ab,de OR 'sf six':ti,ab,de OR sfsix:ti,ab,de OR 'shortform six':ti,ab,de OR 'short form six':ti,ab,de OR QALY:ti,ab,de OR 'quality adjusted life year':ti,ab,de OR 'quality-adjusted life years':ti,ab,de OR 'quality adjusted life-year':ti,ab,de OR 'quality-adjusted life-year':ti,ab,de OR 'quality-adjusted life-year':ti,ab,de OR 'quality of well being':ti,ab,de OR 'quality of well-being':ti,ab,de OR daly:ti,ab,de OR dalys:ti,ab,de OR 'disability adjusted life year':ti,ab,de OR 'disability adjusted life years':ti,ab,de OR 'SF-36':ti,ab,de OR sf36:ti,ab,de OR 'sf 36':ti,ab,de OR 'short form 36':ti,ab,de OR 'shortform 36':ti,ab,de OR 'sf thirtysix':ti,ab,de OR 'sf thirty six':ti,ab,de OR 'shortform thirtysix':ti,ab,de OR 'shortform thirty six':ti,ab,de OR 'short form thirty six':ti,ab,de OR 'short form thirtysix':ti,ab,de OR 'short form thirty six':ti,ab,de OR 'Short Form Health Survey':ti,ab,de OR 'willingness to pay':ti,ab,de OR (utilit*:ti,ab,de AND score*:ti,ab,de) OR (utilit*:ti,ab,de AND weight*:ti,ab,de) OR 'Assessment of Quality of Life':ti,ab,de OR AQOL:ti,ab,de OR 'quality of life':ti OR 'patient reported outcome':ti,ab,de OR 'patient reported outcomes':ti,ab,de OR satisfaction:ti,ab,de OR utilities:ti,ab,de OR disutility:ti,ab,de OR disutilities:ti,ab,de OR 'functional status':ti,ab,de OR 'physical function':ti,ab,de OR 15D:ti,ab,de OR '15-dimensional':ti,ab,de OR '15 dimensional':ti,ab,de OR QWB:ti,ab,de OR 'QWB-SA':ti,ab,de OR 'quality of well being self-	466

Search No.	Search Terms	No. of Articles
	administered':ti,ab,de OR 'quality of well-being self-administered':ti,ab,de OR 'quality of well-being-self-administered':ti,ab,de OR 'quality of well being-self administered':ti,ab,de)	
Exclusions		
#6	'animal'/exp NOT 'human'/exp	3,345,601
#7	Comment*:ti OR Letter:it OR Editorial:it OR 'conference paper':it OR 'conference abstract':it	4,202,161
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7)	475
#9	#8 AND ([english]/lim OR [german]/lim OR [french]/lim)	461

Original Economic Systematic Review - Search Strategy Using Embase to Identify Conference Materials in HER2-Positive Breast Cancer (Conducted on 25 October, 2016)

Search No.	Search Terms	No. of Articles
Disease		
#1	'breast tumor'/exp OR (breast NEXT/1 neoplasm*):ti,ab,de OR (breast NEXT/1 cancer*):ti,ab,de OR (breast NEXT/1 carcinoma*):ti,ab,de OR (breast NEXT/1 tumor*):ti,ab,de OR (breast NEXT/1 tumour*):ti,ab,de OR (mammary NEXT/1 cancer*):ti,ab,de OR (mammary NEXT/1 carcinoma*):ti,ab,de OR (mammary NEXT/1 neoplasm*):ti,ab,de	467,666
Population		
#2	#1 AND (('epidermal growth factor receptor 2'/exp/mj OR 'erbB-2':ti,ab,de OR erbB2:ti,ab,de OR 'erbB 2':ti,ab,de OR 'human epidermal growth factor receptor 2':ti,ab,de OR (oncogene:ti,ab,de AND neu:ti,ab,de) OR HER2*:ti,ab,de OR 'HER-2':ti,ab,de OR 'HER 2':ti,ab,de) AND ('adjuvant chemoradiotherapy'/exp OR 'adjuvant chemotherapy'/exp OR 'adjuvant therapy'/exp OR adjuvant*:ti,ab,de OR neoadjuvant*:ti,ab,de OR (neo NEXT/1 adjuvant*):ti,ab,de))	9,301
Economic Models		
#3	#2 AND ('cost benefit analysis'/exp OR 'statistical model'/exp OR 'cost'/exp OR 'economics'/exp OR 'health economics'/exp OR 'pharmacoeconomics'/exp OR 'cost control'/exp OR (cost NEXT/1 effective*):ti,ab,de OR modeling:ti,ab,de OR modelling:ti,ab,de OR (economic NEXT/1 model*):ti,ab,de OR (model*:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de OR economic*:ti,ab,de OR pharmacoeconomic*:ti,ab,de)) OR Markov:ti,ab,de OR 'decision analysis':ti,ab,de OR 'decision-analytic models':ti,ab,de OR 'cost consequence':ti,ab,de OR ((cost:ti,ab,de OR costs:ti,ab,de) AND (effective*:ti,ab,de OR utilit*:ti,ab,de OR benefit*:ti,ab,de OR minimi*:ti,ab,de)) OR 'discrete event simulation':ti,ab,de OR 'cost analysis':ti,ab,de OR 'cost-analysis':ti,ab,de OR 'cost-minimisation analysis':ti,ab,de OR (economic NEXT/1 benefit*):ti,ab,de OR 'cost utility':ti,ab,de OR 'cost-utility':ti,ab,de OR costminimization:ti,ab,de OR costminimisation:ti,ab,de OR 'cost-minimization':ti,ab,de OR 'cost-minimisation':ti,ab,de OR 'cost minimization':ti,ab,de OR 'cost minimisation':ti,ab,de OR 'budget impact':ti,ab,de OR econometric:ti,ab,de OR 'economic evaluation':ti,ab,de)	543
Cost and Resource Use		
#4	#2 AND ('health care utilization'/exp OR 'fee'/exp OR 'health care cost'/exp OR 'cost of illness'/exp OR 'hospitalization'/exp OR 'length of stay'/exp OR 'drug utilization'/exp OR (('physician'/exp OR 'general practitioner'/exp OR 'emergency treatment'/exp OR 'emergency health service'/exp) AND ('health care utilization'/exp OR 'health economics'/exp)) OR 'absenteeism'/exp OR 'presenteeism'/exp OR 'medical leave'/exp OR 'return to work'/exp OR 'resource use':ti,ab,de OR 'resource utilization':ti,ab,de OR 'resource utilisation':ti,ab,de OR (resource NEXT/1 utili*):ti,ab,de OR 'health care use':ti,ab,de OR 'health service use':ti,ab,de OR 'health services use':ti,ab,de OR 'health care utilization':ti,ab,de OR 'healthcare utilization':ti,ab,de OR 'health care utilisation':ti,ab,de OR 'healthcare utilisation':ti,ab,de OR 'health resource utilization':ti,ab,de OR 'health resource utilisation':ti,ab,de OR 'health service utilization':ti,ab,de OR 'health service utilisation':ti,ab,de OR 'health services utilization':ti,ab,de OR 'health services utilisation':ti,ab,de OR (Economic*:ti AND burden*:ti) OR economic*:ti OR pharmacoeconomic*:ti,ab,de OR (pharmaco NEXT/1 economic*):ti,ab,de OR 'pharmaceutical economics':ti,ab,de OR price*:ti,ab,de OR pricing:ti,ab,de OR cost:ti,ab,de OR costs:ti,ab,de OR budget*:ti,ab,de OR expenditure*:ti,ab,de OR 'health care cost':ti,ab,de OR 'healthcare cost':ti,ab,de OR 'health care costs':ti,ab,de OR 'healthcare costs':ti,ab,de OR 'productivity cost':ti,ab,de OR 'productivity costs':ti,ab,de OR 'societal cost':ti,ab,de OR 'societal costs':ti,ab,de OR ((direct:ti,ab,de OR indirect:ti,ab,de) AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (medication:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (physician:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (hospitalization:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (hospitalisation:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR hospitalization:ti,ab,de OR	518

Search No.	Search Terms	No. of Articles
	hospitalisation:ti,ab,de OR 'hospital visit':ti,ab,de OR medication:ti,ab,de OR 'physician visit':ti,ab,de OR 'GP visit':ti,ab,de OR 'general practitioner visit':ti,ab,de OR 'ED visit':ti,ab,de OR 'emergency department visit':ti,ab,de OR 'emergency room visit':ti,ab,de OR 'ER visit':ti,ab,de OR employ*:ti OR unemploy*:ti OR absenteeism:ti,ab,de OR presenteeism:ti,ab,de OR ('missed work' NEXT/1 day*):ti,ab,de OR 'work absence':ti,ab,de OR 'sickness absence':ti,ab,de OR 'sick leave':ti,ab,de OR 'disability leave':ti,ab,de OR (sick NEXT/1 day*):ti,ab,de OR (illness NEXT/1 day*):ti,ab,de)	
Utility		
#5	#2 AND ('quality of life'/exp OR 'quality adjusted life year'/exp OR 'health utility':ti,ab,de OR 'health utilities':ti,ab,de OR productivity:ti,ab,de OR EuroQol:ti,ab,de OR 'standard gamble':ti,ab,de OR 'time trade off':ti,ab,de OR 'time trade-off':ti,ab,de OR 'time tradeoff':ti,ab,de OR TTO:ti,ab,de OR EQ5D:ti,ab,de OR 'EQ-5D':ti,ab,de OR 'EQ 5D':ti,ab,de OR 'EuroQoL 5D':ti,ab,de OR EORTC:ti,ab,de OR 'health utility index':ti,ab,de OR 'health utilities index':ti,ab,de OR (health:ti,ab,de AND utilit*:ti,ab,de AND index:ti,ab,de) OR HUI:ti,ab,de OR 'SF-6D':ti,ab,de OR sf6*:ti,ab,de OR 'sf 6':ti,ab,de OR 'short form 6':ti,ab,de OR 'shortform 6':ti,ab,de OR 'sf six':ti,ab,de OR sfsix:ti,ab,de OR 'shortform six':ti,ab,de OR 'short form six':ti,ab,de OR QALY:ti,ab,de OR 'quality adjusted life year':ti,ab,de OR 'quality-adjusted life years':ti,ab,de OR 'quality adjusted life-year':ti,ab,de OR 'quality-adjusted life-year':ti,ab,de OR 'quality-adjusted life-year':ti,ab,de OR 'quality of well being':ti,ab,de OR 'quality of well-being':ti,ab,de OR daly:ti,ab,de OR dalys:ti,ab,de OR 'disability adjusted life year':ti,ab,de OR 'disability adjusted life years':ti,ab,de OR 'SF-36':ti,ab,de OR sf36:ti,ab,de OR 'sf 36':ti,ab,de OR 'short form 36':ti,ab,de OR 'shortform 36':ti,ab,de OR 'sf thirtysix':ti,ab,de OR 'sf thirty six':ti,ab,de OR 'shortform thirtysix':ti,ab,de OR 'shortform thirty six':ti,ab,de OR 'short form thirty six':ti,ab,de OR 'short form thirtysix':ti,ab,de OR 'short form thirty six':ti,ab,de OR 'Short Form Health Survey':ti,ab,de OR 'willingness to pay':ti,ab,de OR (utilit*:ti,ab,de AND score*:ti,ab,de) OR (utilit*:ti,ab,de AND weight*:ti,ab,de) OR 'Assessment of Quality of Life':ti,ab,de OR AQOL:ti,ab,de OR 'quality of life':ti OR 'patient reported outcome':ti,ab,de OR 'patient reported outcomes':ti,ab,de OR satisfaction:ti,ab,de OR utilities:ti,ab,de OR disutility:ti,ab,de OR disutilities:ti,ab,de OR 'functional status':ti,ab,de OR 'physical function':ti,ab,de OR 15D:ti,ab,de OR '15-dimensional':ti,ab,de OR '15 dimensional':ti,ab,de OR QWB:ti,ab,de OR 'QWB-SA':ti,ab,de OR 'quality of well being self-administered':ti,ab,de OR 'quality of well-being self-administered':ti,ab,de OR 'quality of well-being-self-administered':ti,ab,de OR 'quality of well being-self administered':ti,ab,de)	466
Exclusions		
#6	'animal'/exp NOT 'human'/exp	3,345,601
#7	Comment*:ti OR Letter:it OR Editorial:it	1,187,394
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7)	1,013
#9	#8 AND ([english]/lim OR [german]/lim OR [french]/lim)	999
#10	#9 AND ('conference paper':it OR 'conference abstract':it)	538
#11	#10 AND ('10th european breast cancer conference, ebcc-10':nc OR '14th st. gallen international breast cancer conference: primary therapy of early breast cancer':nc OR '2015 annual meeting of the american society of clinical oncology, asco':nc OR '2016 annual meeting of the american society of clinical oncology, asco 2016':nc OR '38th annual ctrc-aacr san antonio breast cancer symposium':nc OR 'asco`s quality care symposium 2016':nc OR 'ispor 18th annual european congress':nc OR 'ispor 21st annual international meeting research':nc)	74

Original Economic Systematic Review - EconLit Literature Search Strategy (Conducted on 25 October, 2016)

Search No.	Search Terms	No. of Articles
Disease		
#1	"breast neoplasm*" OR "breast cancer*" OR "breast carcinoma*" OR "breast tumor*" OR "breast tumour*" OR "mammary cancer*" OR "mammary carcinoma*" OR "mammary neoplasm*"	248
Population		
#2	#1 AND (("ErbB-2 Receptor" OR "erbB-2" OR erbB2 OR "erbB 2" OR "human epidermal growth factor receptor 2" OR (oncogene AND neu) OR "HER2*" OR "HER-2*" OR "HER 2*") AND ("Adjuvant Chemoradiotherapy" OR "Adjuvant Chemotherapy" OR "Neoadjuvant Therapy" OR adjuvant* OR neoadjuvant* OR "neo-adjuvant*"))	0
Economic Models		

Search No.	Search Terms	No. of Articles
#3	#2 AND (“Cost-Benefit Analysis” OR “Models, Economic” OR “Models, Econometric” OR “Costs and Cost Analysis” OR “Economics” OR “Economics, Hospital” OR “Economics, Medical” OR “Economics, Nursing” OR “Economics, Pharmaceutical” OR “Cost Savings” OR cost effective* OR cost-effective* OR modeling OR modelling OR economic model* OR (model* AND (cost OR costs OR economic* OR pharmacoeconomic*)) OR Markov OR “decision analysis” OR “decision-analytic models” OR “cost consequence” OR ((cost OR costs) AND (effective* OR utilit* OR benefit* OR minimi*)) OR “discrete event simulation” OR “cost analysis” OR “cost-analysis” OR “cost-minimisation analysis” OR economic benefit* OR “cost utility” OR “cost-utility” OR costminimization OR costminimisation OR “cost-minimization” OR “cost-minimisation” OR “cost minimization” OR “cost minimisation” OR “budget impact” OR econometric OR “economic evaluation”)	0
Cost and Resource Use		
#4	#2 AND (“Health Resources/utilization” OR “Fees and Charges” OR “Health Care Costs” OR “Cost of Illness” OR “Health Expenditures” OR “Hospitalization” OR “Length of Stay” OR “Drug Utilization” OR “Physicians/economics” OR “Physicians/utilization” OR “General Practitioners/economics” OR “General Practitioners/utilization” OR “Emergency Treatment/economics” OR “Emergency Treatment/utilization” OR “Emergency Service, Hospital/economics” OR “Emergency Service, Hospital/utilization” OR “Absenteeism” OR “Presenteeism” OR “Sick Leave” OR “Return to Work” OR “resource use” OR “resource utilization” OR “resource utilisation” OR resource utili* OR “health care use” OR “health service use” OR “health services use” OR “health care utilization” OR “healthcare utilization” OR “health care utilisation” OR “healthcare utilisation” OR “health resource utilization” OR “health resource utilisation” OR “health service utilization” OR “health service utilisation” OR “health services utilization” OR “health services utilisation” OR (Economic* AND burden*) OR economic* OR pharmacoeconomic* OR pharmaco economic* OR “pharmaceutical economics” OR price* OR pricing OR cost OR costs OR budget* OR expenditure* OR “health care cost” OR “healthcare cost” OR “health care costs” OR “healthcare costs” OR “productivity cost” OR “productivity costs” OR “societal cost” OR “societal costs” OR ((direct OR indirect) AND (cost OR costs)) OR (medication AND (cost OR costs)) OR (physician AND (cost OR costs)) OR (hospitalization AND (cost OR costs)) OR (hospitalisation AND (cost OR costs)) OR hospitalization OR hospitalisation OR “hospital visit” OR medication OR “physician visit” OR “GP visit” OR “general practitioner visit” OR “ED visit” OR “emergency department visit” OR “emergency room visit” OR “ER visit” OR employ* OR unemploy* OR absenteeism OR presenteeism OR missed work day* OR “work absence” OR “sickness absence” OR “sick leave” OR “disability leave” OR sick day* OR illness day*)	0
Utility		
#5	#2 AND (“Quality of Life” OR “Quality-Adjusted Life Years” OR “health utility” OR “health utilities” OR productivity OR “EuroQol” OR “standard gamble” OR “time trade off” OR “time trade-off” OR “time tradeoff” OR “TTO” OR “EQ5D” OR “EQ-5D” OR “EQ 5D” OR “EuroQoL 5D” OR “EORTC” OR “health utility index” OR “health utilities index” OR (health AND utilit* AND index) OR “HUI” OR “SF-6D” OR sf6* OR sf 6* OR short form 6* OR shortform 6* OR “sf six” OR “sfsix” OR “shortform six” OR “short form six” OR “QALY” OR “quality adjusted life year” OR “quality-adjusted life years” OR “quality adjusted life-year” OR “quality-adjusted life-year” OR “quality-adjusted life-year” OR “quality of well being” OR “quality of well-being” OR “daly” OR “dalys” OR “disability adjusted life year” OR “disability adjusted life years” OR “SF-36” OR “sf36” OR “sf 36” OR “short form 36” OR “shortform 36” OR “sf thirtysix” OR “sf thirty six” OR “shortform thirtysix” OR “shortform thirty six” OR “short form thirty six” OR “short form thirtysix” OR “short form thirty six” OR “Short Form Health Survey” OR “willingness to pay” OR (utilit* AND score*) OR (utilit* AND weight*) OR “Assessment of Quality of Life” OR “AQOL” OR “quality of life” OR “patient reported outcome” OR “patient reported outcomes” OR satisfaction OR utilities OR disutility OR disutilities OR “functional status” OR “physical function” OR “15D” OR “15-dimensional” OR “15 dimensional” OR “QWB” OR “QWB-SA” OR “quality of well being self-administered” OR “quality of well-being self-administered” OR “quality of well-being-self-administered” OR “quality of well being-self administered”)	0
Exclusions		
#6	SU animal* NOT SU human*	161
#7	TI (Comment* OR Letter OR Editorial)	38,395
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7)	0
#9	#8 AND (ZL "english" OR ZL "german" OR ZL "french")	0

Original Economic Systematic Review - BIOSIS Literature Search Strategy (Conducted on 25 October, 2016)

Search No.	Search Terms	No. of Articles
Disease		
#1	ti,ab,su(breast P/0 neoplasm* OR breast P/0 cancer* OR breast P/0 carcinoma* OR breast p/0 tumor* OR breast P/0 tumour* OR mammary P/0 cancer* OR mammary P/0 carcinoma* OR mammary P/0 neoplasm*)	277,327
Population		
#2	#1 AND ti,ab,su("erbB-2" OR erbB2 OR "erbB 2" OR "human epidermal growth factor receptor 2" OR (oncogene AND neu) OR HER2* OR HER P/0 2) AND (su("Chemoradiotherapy Adjuvant" OR "Chemotherapy Adjuvant" OR "Neoadjuvant Therapy") OR ti,ab,su(adjuvant* OR neoadjuvant* OR neo P/0 adjuvant*))	2,514
Economic Models		
#3	#2 AND (su("Cost-Benefit Analysis" OR "Models Economic" OR "Models Econometric" OR "Costs and Cost Analysis" OR Economics OR "Economics Hospital" OR "Economics Medical" OR "Economics Nursing" OR "Economics Pharmaceutical" OR "Cost Savings") OR ti,ab,su(cost P/0 effective* OR modeling OR modelling OR economic P/0 model* OR (model* AND (cost OR costs OR economic* OR pharmacoeconomic*)) OR Markov OR "decision analysis" OR "decision-analytic models" OR "cost consequence" OR ((cost OR costs) AND (effective* OR utilit* OR benefit* OR minimi*)) OR "discrete event simulation" OR "cost analysis" OR "cost-analysis" OR "cost-minimisation analysis" OR economic P/0 benefit* OR "cost utility" OR "cost-utility" OR costminimization OR costminimisation OR "cost-minimization" OR "cost-minimisation" OR "cost minimization" OR "cost minimisation" OR "budget impact" OR econometric OR "economic evaluation"))	65
Cost and Resource Use		
#4	#2 AND (su("Health Resources" P/0 utilization OR Fees P/1 Charges OR "Health Care Costs" OR "Cost of Illness" OR "Health Expenditures" OR Hospitalization OR "Length of Stay" OR "Drug Utilization" OR Physicians P/0 economics OR Physicians P/0 utilization OR "General Practitioners" P/0 economics OR "General Practitioners" P/0 utilization OR "Emergency Treatment" P/0 economics OR "Emergency Treatment" P/0 utilization OR "Emergency Service Hospital" P/0 economics OR "Emergency Service Hospital" P/0 utilization OR Absenteeism OR Presenteeism OR "Sick Leave" OR "Return to Work") OR ti,ab,su("resource use" OR "resource utilization" OR "resource utilisation" OR resource P/0 utili* OR "health care use" OR "health service use" OR "health services use" OR "health care utilization" OR "healthcare utilization" OR "health care utilisation" OR "healthcare utilisation" OR "health resource utilization" OR "health resource utilisation" OR "health service utilization" OR "health service utilisation" OR "health services utilization" OR "health services utilisation" OR pharmacoeconomic* OR pharmaco P/0 economic* OR "pharmaceutical economics" OR price* OR pricing OR cost OR costs OR budget* OR expenditure* OR "health care cost" OR "healthcare cost" OR "health care costs" OR "healthcare costs" OR "productivity cost" OR "productivity costs" OR "societal cost" OR "societal costs" OR ((direct OR indirect) AND (cost OR costs)) OR (medication AND (cost OR costs)) OR (physician AND (cost OR costs)) OR (hospitalization AND (cost OR costs)) OR (hospitalisation AND (cost OR costs)) OR hospitalization OR hospitalisation OR "hospital visit" OR medication OR "physician visit" OR "GP visit" OR "general practitioner visit" OR "ED visit" OR "emergency department visit" OR "emergency room visit" OR "ER visit" OR absenteeism OR presenteeism OR "missed work" P/0 day* OR "work absence" OR "sickness absence" OR "sick leave" OR "disability leave" OR sick P/0 day* OR illness P/0 day*) OR ti((Economic* AND burden*) OR economic* OR employ* OR unemploy*))	76
Utility		
#5	#2 AND (su("Quality of Life" OR "Quality-Adjusted Life Years") OR ti,ab,su("health utility" OR "health utilities" OR productivity OR EuroQol OR "standard gamble" OR "time trade off" OR "time trade-off" OR "time tradeoff" OR TTO OR EQ5D OR "EQ-5D" OR "EQ 5D" OR "EuroQoL 5D" OR EORTC OR "health utility index" OR "health utilities index" OR (health AND utilit* AND index) OR HUI OR "SF-6D" OR sf6* OR sf P/0 6 OR "short form" P/0 6 OR shortform P/0 6 OR "sf six" OR sfsix OR "shortform six" OR "short form six" OR QALY OR "quality adjusted life year" OR "quality-adjusted life years" OR "quality adjusted life-year" OR "quality-adjusted life-year" OR "quality-adjusted life-year" OR "quality of well being" OR "quality of well-being" OR daly OR dalys OR "disability adjusted life year" OR "disability adjusted life years" OR "SF-36" OR sf36 OR "sf 36" OR "short form 36" OR "shortform 36" OR "sf thirtysix" OR "sf thirty six" OR "shortform thirtysix" OR "shortform thirty six" OR "short form thirty six" OR "short form thirtysix" OR "short form thirty six" OR "Short Form Health Survey" OR "willingness to pay" OR (utilit* AND score*) OR (utilit* AND weight*) OR "Assessment of Quality of Life" OR AQOL OR "patient reported outcome" OR	96

Search No.	Search Terms	No. of Articles
	"patient reported outcomes" OR satisfaction OR utilities OR disutility OR disutilities OR "functional status" OR "physical function" OR 15D OR "15-dimensional" OR "15 dimensional" OR QWB OR "QWB-SA" OR "quality of well being self-administered" OR "quality of well-being self-administered" OR "quality of well-being-self-administered" OR "quality of well being-self administered") OR ti("quality of life"))	
Exclusions		
#6	su(animal) NOT su(human)	8,399,231
#7	dtype(Comment* OR Letter OR Editorial)	184,946
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7)	163
#9	#8 AND la(English OR German OR French)	162

Original Economic Systematic Review - Cochrane Literature Search Strategy (Conducted on 25 October, 2016)

Search No.	Search Terms	No. of Articles
Disease		
#1	#1 MeSH descriptor: [Breast Neoplasms] explode all trees 9857 #2 breast next neoplasm* or breast next cancer* or breast next carcinoma* or breast next tumor* or breast next tumour* or mammary next cancer* or mammary next carcinoma* or mammary next neoplasm*:ti,ab,kw (Word variations have been searched) 21821 #3 #1 or #2 21828	21,828
Population		
#2	#4 MeSH descriptor: [Receptor, ErbB-2] explode all trees 596 #5 "erbB-2" or erbB2 or "erbB 2" or "human epidermal growth factor receptor 2" or (oncogene and neu) or HER2* or HER next 2*:ti,ab,kw (Word variations have been searched) 4756 #6 MeSH descriptor: [Chemoradiotherapy, Adjuvant] explode all trees 112 #7 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees 3724 #8 MeSH descriptor: [Neoadjuvant Therapy] explode all trees 950 #9 adjuvant* or neoadjuvant* or neo next adjuvant*:ti,ab,kw (Word variations have been searched)21125 #10 #3 and (#4 or #5) and (#6 or #7 or #8 or #9) 1041	1,041
Economic Models		
#3	#11 MeSH descriptor: [Cost-Benefit Analysis] explode all trees 17955 #12 MeSH descriptor: [Models, Economic] explode all trees 2000 #13 MeSH descriptor: [Models, Econometric] explode all trees 453 #14 MeSH descriptor: [Costs and Cost Analysis] explode all trees 24871 #15 MeSH descriptor: [Economics] explode all trees 26895 #16 MeSH descriptor: [Economics, Hospital] explode all trees 1750 #17 MeSH descriptor: [Economics, Medical] explode all trees 105 #18 MeSH descriptor: [Economics, Nursing] explode all trees 19 #19 MeSH descriptor: [Economics, Pharmaceutical] explode all trees 243 #20 MeSH descriptor: [Cost Savings] explode all trees 995 #21 cost next effective* or modeling or modelling or economic next model* or (model* and (cost or costs or economic* or pharmacoeconomic*)) or Markov or "decision analysis" or "decision-analytic models" or "cost consequence" or ((cost or costs) and (effective* or utilit* or benefit* or minimi*)) or "discrete event simulation" or "cost analysis" or "cost-analysis" or "cost-minimisation analysis" or economic next benefit* or "cost utility" or "cost-utility" or costminimization or costminimisation or "cost-minimization" or "cost-minimisation" or "cost minimization" or "cost minimisation" or "budget impact" or econometric or "economic evaluation":ti,ab,kw (Word variations have been searched) 105158 #22 #10 and (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21) 198	198
Cost and Resource Use		
#4	#23 MeSH descriptor: [Health Resources] explode all trees and with qualifier(s): [Utilization - UT] 407 #24 MeSH descriptor: [Fees and Charges] explode all trees 504 #25 MeSH descriptor: [Health Care Costs] explode all trees 7234 #26 MeSH descriptor: [Cost of Illness] explode all trees 1291 #27 MeSH descriptor: [Health Expenditures] explode all trees 324 #28 MeSH descriptor: [Hospitalization] explode all trees 14021 #29 MeSH descriptor: [Length of Stay] explode all trees 7569	73

Search No.	Search Terms	No. of Articles
	#30 MeSH descriptor: [Drug Utilization] explode all trees 561 #31 MeSH descriptor: [Physicians] explode all trees and with qualifier(s): [Economics - EC] 62 #32 MeSH descriptor: [Physicians] explode all trees and with qualifier(s): [Utilization - UT] 25 #33 MeSH descriptor: [General Practitioners] explode all trees and with qualifier(s): [Economics - EC] 3 #34 MeSH descriptor: [General Practitioners] explode all trees and with qualifier(s): [Utilization - UT] 2 #35 MeSH descriptor: [Emergency Treatment] explode all trees and with qualifier(s): [Economics - EC] 129 #36 MeSH descriptor: [Emergency Treatment] explode all trees and with qualifier(s): [Utilization - UT] 46 #37 MeSH descriptor: [Emergency Service, Hospital] explode all trees and with qualifier(s): [Economics - EC] 229 #38 MeSH descriptor: [Emergency Service, Hospital] explode all trees and with qualifier(s): [Utilization - UT] 261 #39 MeSH descriptor: [Absenteeism] explode all trees 492 #40 MeSH descriptor: [Presenteeism] explode all trees 3 #41 MeSH descriptor: [Sick Leave] explode all trees 500 #42 MeSH descriptor: [Return to Work] explode all trees 107 #43 (Economic* and burden*) or economic* or employ* or unemploy*:ti or "resource use" or "resource utilization" or "resource utilisation" or resource next utili* or "health care use" or "health service use" or "health services use" or "health care utilization" or "healthcare utilization" or "health care utilisation" or "healthcare utilisation" or "health resource utilization" or "health resource utilisation" or "health service utilization" or "health service utilisation" or "health services utilization" or "health services utilisation" or pharmacoeconomic* or pharmaco next economic* or "pharmaceutical economics" or price* or pricing or cost or costs or budget* or expenditure* or "health care cost" or "healthcare cost" or "health care costs" or "healthcare costs" or "productivity cost" or "productivity costs" or "societal cost" or "societal costs" or ((direct or indirect) and (cost or costs)) or (medication and (cost or costs)) or (physician and (cost or costs)) or (hospitalization and (cost or costs)) or (hospitalisation and (cost or costs)) or hospitalization or hospitalisation or "hospital visit" or medication or "physician visit" or "GP visit" or "general practitioner visit" or "ED visit" or "emergency department visit" or "emergency room visit" or "ER visit" or absenteeism or presenteeism or "missed work" next day* or "work absence" or "sickness absence" or "sick leave" or "disability leave" or sick next day* or illness next day*:ti,ab,kw (Word variations have been searched) 113352 #44 #10 and (#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43) 73	
Utility		
#5	#45 MeSH descriptor: [Quality of Life] explode all trees 18482 #46 MeSH descriptor: [Quality-Adjusted Life Years] explode all trees 4131 #47 "quality of life":ti or "health utility" or "health utilities" or productivity or EuroQol or "standard gamble" or "time trade off" or "time trade-off" or "time tradeoff" or TTO or EQ5D or "EQ-5D" or "EQ 5D" or "EuroQoL 5D" or EORTC or "health utility index" or "health utilities index" or (health and utilit* and index) or HUI or "SF-6D" or sf6* or sf next 6* or "short form" next 6* or shortform next 6* or "sf six" or sfsix or "shortform six" or "short form six" or QALY or "quality adjusted life year" or "quality-adjusted life years" or "quality adjusted life-year" or "quality-adjusted life-year" or "quality-adjusted life-year" or "quality of well being" or "quality of well-being" or daly or dalys or "disability adjusted life year" or "disability adjusted life years" or "SF-36" or sf36 or "sf 36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six" or "Short Form Health Survey" or "willingness to pay" or (utilit* and score*) or (utilit* and weight*) or "Assessment of Quality of Life" or AQOL or "patient reported outcome" or "patient reported outcomes" or satisfaction or utilities or disutility or disutilities or "functional status" or "physical function" or 15D or "15-dimensional" or "15 dimensional" or QWB or "QWB-SA" or "quality of well being self-administered" or "quality of well-being self-administered" or "quality of well-being-self-administered" or "quality of well being-self administered":ti,ab,kw (Word variations have been searched) 60382 #48 #10 and (#45 or #46 or #47) 86	86
Exclusions		
#6	#49 MeSH descriptor: [Animals] explode all trees 7686 #50 MeSH descriptor: [Humans] explode all trees 1343	6,343

Search No.	Search Terms	No. of Articles
	#51 #49 not #50 6343	
#7	#52 Comment or Letter or Editorial:pt (Word variations have been searched) 7901	7,901
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7) Cochrane Reviews - 4 (4 imported) Other Reviews -2 (2 imported) Trials – 255 (193 imported) Methods Studies -2 (1 imported) Economic Evaluations – 16 (16 imported)	279

First Update - Search Strategy Using Embase to Identify Economic Studies of HER2+ Breast Cancer (Conducted on 19 February, 2018)

Search No.	Search Terms	No. of Articles
Disease		
#1	'breast tumor'/exp OR (breast NEXT/1 neoplasm*):ti,ab,de OR (breast NEXT/1 cancer*):ti,ab,de OR (breast NEXT/1 carcinoma*):ti,ab,de OR (breast NEXT/1 tumor*):ti,ab,de OR (breast NEXT/1 tumour*):ti,ab,de OR (mammary NEXT/1 cancer*):ti,ab,de OR (mammary NEXT/1 carcinoma*):ti,ab,de OR (mammary NEXT/1 neoplasm*):ti,ab,de	520,402
Population		
#2	#1 AND (('epidermal growth factor receptor 2'/exp/mj OR 'erbB-2':ti,ab,de OR erbB2:ti,ab,de OR 'erbB 2':ti,ab,de OR 'human epidermal growth factor receptor 2':ti,ab,de OR (oncogene:ti,ab,de AND neu:ti,ab,de) OR HER2*:ti,ab,de OR 'HER-2':ti,ab,de OR 'HER 2':ti,ab,de) AND ('adjuvant chemoradiotherapy'/exp OR 'adjuvant chemotherapy'/exp OR 'adjuvant therapy'/exp OR adjuvant*:ti,ab,de OR neoadjuvant*:ti,ab,de OR (neo NEXT/1 adjuvant*):ti,ab,de))	11,593
Economic Models		
#3	#2 AND ('cost benefit analysis'/exp OR 'statistical model'/exp OR 'cost'/exp OR 'economics'/exp OR 'health economics'/exp OR 'pharmacoeconomics'/exp OR 'cost control'/exp OR (cost NEXT/1 effective*):ti,ab,de OR modeling:ti,ab,de OR modelling:ti,ab,de OR (economic NEXT/1 model*):ti,ab,de OR (model*:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de OR economic*:ti,ab,de OR pharmacoeconomic*:ti,ab,de)) OR Markov:ti,ab,de OR 'decision analysis':ti,ab,de OR 'decision-analytic models':ti,ab,de OR 'cost consequence':ti,ab,de OR ((cost:ti,ab,de OR costs:ti,ab,de) AND (effective*:ti,ab,de OR utilit*:ti,ab,de OR benefit*:ti,ab,de OR minimi*:ti,ab,de)) OR 'discrete event simulation':ti,ab,de OR 'cost analysis':ti,ab,de OR 'cost-analysis':ti,ab,de OR 'cost-minimisation analysis':ti,ab,de OR (economic NEXT/1 benefit*):ti,ab,de OR 'cost utility':ti,ab,de OR 'cost-utility':ti,ab,de OR costminimization:ti,ab,de OR costminimisation:ti,ab,de OR 'cost-minimization':ti,ab,de OR 'cost-minimisation':ti,ab,de OR 'cost minimization':ti,ab,de OR 'cost minimisation':ti,ab,de OR 'budget impact':ti,ab,de OR econometric:ti,ab,de OR 'economic evaluation':ti,ab,de)	696
Cost and Resource Use		
#4	#2 AND ('health care utilization'/exp OR 'fee'/exp OR 'health care cost'/exp OR 'cost of illness'/exp OR 'hospitalization'/exp OR 'length of stay'/exp OR 'drug utilization'/exp OR (('physician'/exp OR 'general practitioner'/exp OR 'emergency treatment'/exp OR 'emergency health service'/exp) AND ('health care utilization'/exp OR 'health economics'/exp)) OR 'absenteeism'/exp OR 'presenteeism'/exp OR 'medical leave'/exp OR 'return to work'/exp OR 'resource use':ti,ab,de OR 'resource utilization':ti,ab,de OR 'resource utilisation':ti,ab,de OR (resource NEXT/1 utili*):ti,ab,de OR 'health care use':ti,ab,de OR 'health service use':ti,ab,de OR 'health services use':ti,ab,de OR 'health care utilization':ti,ab,de OR 'healthcare utilization':ti,ab,de OR 'health care utilisation':ti,ab,de OR 'healthcare utilisation':ti,ab,de OR 'health resource utilization':ti,ab,de OR 'health resource utilisation':ti,ab,de OR 'health service utilization':ti,ab,de OR 'health service utilisation':ti,ab,de OR 'health services utilization':ti,ab,de OR 'health services utilisation':ti,ab,de OR (Economic*:ti AND burden*:ti) OR economic*:ti OR pharmacoeconomic*:ti,ab,de OR (pharmaco NEXT/1 economic*):ti,ab,de OR 'pharmaceutical economics':ti,ab,de OR price*:ti,ab,de OR pricing:ti,ab,de OR cost:ti,ab,de OR costs:ti,ab,de OR budget*:ti,ab,de OR expenditure*:ti,ab,de OR 'health care cost':ti,ab,de OR 'healthcare cost':ti,ab,de OR 'health care costs':ti,ab,de OR 'healthcare costs':ti,ab,de OR 'productivity cost':ti,ab,de OR 'productivity costs':ti,ab,de OR 'societal cost':ti,ab,de OR 'societal costs':ti,ab,de OR ((direct:ti,ab,de OR indirect:ti,ab,de) AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (medication:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (physician:ti,ab,de AND	629

Search No.	Search Terms	No. of Articles
	(cost:ti,ab,de OR costs:ti,ab,de)) OR (hospitalization:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (hospitalisation:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR hospitalization:ti,ab,de OR hospitalisation:ti,ab,de OR 'hospital visit':ti,ab,de OR medication:ti,ab,de OR 'physician visit':ti,ab,de OR 'GP visit':ti,ab,de OR 'general practitioner visit':ti,ab,de OR 'ED visit':ti,ab,de OR 'emergency department visit':ti,ab,de OR 'emergency room visit':ti,ab,de OR 'ER visit':ti,ab,de OR employ*:ti OR unemploy*:ti OR absenteeism:ti,ab,de OR presenteeism:ti,ab,de OR ('missed work' NEXT/1 day*):ti,ab,de OR 'work absence':ti,ab,de OR 'sickness absence':ti,ab,de OR 'sick leave':ti,ab,de OR 'disability leave':ti,ab,de OR (sick NEXT/1 day*):ti,ab,de OR (illness NEXT/1 day*):ti,ab,de)	
Utility		
#5	#2 AND ('quality of life'/exp OR 'quality adjusted life year'/exp OR 'health utility':ti,ab,de OR 'health utilities':ti,ab,de OR productivity:ti,ab,de OR EuroQol:ti,ab,de OR 'standard gamble':ti,ab,de OR 'time trade off':ti,ab,de OR 'time trade-off':ti,ab,de OR 'time tradeoff':ti,ab,de OR TTO:ti,ab,de OR EQ5D:ti,ab,de OR 'EQ-5D':ti,ab,de OR 'EQ 5D':ti,ab,de OR 'EuroQoL 5D':ti,ab,de OR EORTC:ti,ab,de OR 'health utility index':ti,ab,de OR 'health utilities index':ti,ab,de OR (health:ti,ab,de AND utilit*:ti,ab,de AND index:ti,ab,de) OR HUI:ti,ab,de OR 'SF-6D':ti,ab,de OR sf6*:ti,ab,de OR 'sf 6':ti,ab,de OR 'short form 6':ti,ab,de OR 'shortform 6':ti,ab,de OR 'sf six':ti,ab,de OR sfsix:ti,ab,de OR 'shortform six':ti,ab,de OR 'short form six':ti,ab,de OR QALY:ti,ab,de OR 'quality adjusted life year':ti,ab,de OR 'quality-adjusted life years':ti,ab,de OR 'quality adjusted life-year':ti,ab,de OR 'quality-adjusted life-year':ti,ab,de OR 'quality-adjusted life-year':ti,ab,de OR 'quality of well being':ti,ab,de OR 'quality of well-being':ti,ab,de OR daly:ti,ab,de OR dalys:ti,ab,de OR 'disability adjusted life year':ti,ab,de OR 'disability adjusted life years':ti,ab,de OR 'SF-36':ti,ab,de OR sf36:ti,ab,de OR 'sf 36':ti,ab,de OR 'short form 36':ti,ab,de OR 'shortform 36':ti,ab,de OR 'sf thirtysix':ti,ab,de OR 'sf thirty six':ti,ab,de OR 'shortform thirtysix':ti,ab,de OR 'shortform thirty six':ti,ab,de OR 'short form thirty six':ti,ab,de OR 'short form thirtysix':ti,ab,de OR 'short form thirty six':ti,ab,de OR 'Short Form Health Survey':ti,ab,de OR 'willingness to pay':ti,ab,de OR (utilit*:ti,ab,de AND score*:ti,ab,de) OR (utilit*:ti,ab,de AND weight*:ti,ab,de) OR 'Assessment of Quality of Life':ti,ab,de OR AQOL:ti,ab,de OR 'quality of life':ti OR 'patient reported outcome':ti,ab,de OR 'patient reported outcomes':ti,ab,de OR satisfaction:ti,ab,de OR utilities:ti,ab,de OR disutility:ti,ab,de OR disutilities:ti,ab,de OR 'functional status':ti,ab,de OR 'physical function':ti,ab,de OR 15D:ti,ab,de OR '15-dimensional':ti,ab,de OR '15 dimensional':ti,ab,de OR QWB:ti,ab,de OR 'QWB-SA':ti,ab,de OR 'quality of well being self-administered':ti,ab,de OR 'quality of well-being self-administered':ti,ab,de OR 'quality of well-being-self-administered':ti,ab,de OR 'quality of well being-self administered':ti,ab,de)	586
Exclusions		
#6	'animal'/exp NOT 'human'/exp	4,990,740
#7	Comment*:ti OR Letter:it OR Editorial:it OR 'conference paper':it OR 'conference abstract':it	5,281,247
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7)	596
#9	#8 AND ([english]/lim OR [german]/lim OR [french]/lim)	575
#10	#8 AND ([english]/lim OR [german]/lim OR [french]/lim) AND [9-8-2016]/sd NOT [28-02-2018]/sd	107

First Update - Search Strategy Using EconLit to Identify Economic Studies of HER2+ Breast Cancer (Conducted on 19 February, 2018)

Search No.	Search Terms	No. of Articles
Disease		
#1	"breast neoplasm*" OR "breast cancer*" OR "breast carcinoma*" OR "breast tumor*" OR "breast tumour*" OR "mammary cancer*" OR "mammary carcinoma*" OR "mammary neoplasm*"	266
Population		
#2	#1 AND (("ErbB-2 Receptor" OR "erbB-2" OR erbB2 OR "erbB 2" OR "human epidermal growth factor receptor 2" OR (oncogene AND neu) OR "HER2*" OR "HER-2*" OR "HER 2*") AND ("Adjuvant Chemoradiotherapy" OR "Adjuvant Chemotherapy" OR "Neoadjuvant Therapy" OR adjuvant* OR neoadjuvant* OR "neo-adjuvant*"))	0
Economic Models		
#3	#2 AND ("Cost-Benefit Analysis" OR "Models, Economic" OR "Models, Econometric" OR "Costs and Cost Analysis" OR "Economics" OR "Economics, Hospital" OR "Economics, Medical" OR "Economics, Nursing" OR "Economics, Pharmaceutical" OR "Cost Savings" OR cost effective* OR cost-effective* OR modeling OR modelling OR economic model* OR (model* AND (cost OR costs OR economic* OR pharmacoeconomic*)) OR Markov OR "decision analysis" OR "decision-analytic	0

Search No.	Search Terms	No. of Articles
	models" OR "cost consequence" OR ((cost OR costs) AND (effective* OR utilit* OR benefit* OR minimi*)) OR "discrete event simulation" OR "cost analysis" OR "cost-analysis" OR "cost-minimisation analysis" OR economic benefit* OR "cost utility" OR "cost-utility" OR costminimization OR costminimisation OR "cost-minimization" OR "cost-minimisation" OR "cost minimization" OR "cost minimisation" OR "budget impact" OR econometric OR "economic evaluation")	
Cost and Resource Use		
#4	#2 AND ("Health Resources/utilization" OR "Fees and Charges" OR "Health Care Costs" OR "Cost of Illness" OR "Health Expenditures" OR "Hospitalization" OR "Length of Stay" OR "Drug Utilization" OR "Physicians/economics" OR "Physicians/utilization" OR "General Practitioners/economics" OR "General Practitioners/utilization" OR "Emergency Treatment/economics" OR "Emergency Treatment/utilization" OR "Emergency Service, Hospital/economics" OR "Emergency Service, Hospital/utilization" OR "Absenteeism" OR "Presenteeism" OR "Sick Leave" OR "Return to Work" OR "resource use" OR "resource utilization" OR "resource utilisation" OR resource utili* OR "health care use" OR "health service use" OR "health services use" OR "health care utilization" OR "healthcare utilization" OR "health care utilisation" OR "healthcare utilisation" OR "health resource utilization" OR "health resource utilisation" OR "health service utilization" OR "health service utilisation" OR "health services utilization" OR "health services utilisation" OR (Economic* AND burden*) OR economic* OR pharmacoeconomic* OR pharmaco economic* OR "pharmaceutical economics" OR price* OR pricing OR cost OR costs OR budget* OR expenditure* OR "health care cost" OR "healthcare cost" OR "health care costs" OR "healthcare costs" OR "productivity cost" OR "productivity costs" OR "societal cost" OR "societal costs" OR ((direct OR indirect) AND (cost OR costs)) OR (medication AND (cost OR costs)) OR (physician AND (cost OR costs)) OR (hospitalization AND (cost OR costs)) OR (hospitalisation AND (cost OR costs)) OR hospitalization OR hospitalisation OR "hospital visit" OR medication OR "physician visit" OR "GP visit" OR "general practitioner visit" OR "ED visit" OR "emergency department visit" OR "emergency room visit" OR "ER visit" OR employ* OR unemploy* OR absenteeism OR presenteeism OR missed work day* OR "work absence" OR "sickness absence" OR "sick leave" OR "disability leave" OR sick day* OR illness day*)	0
Utility		
#5	#2 AND ("Quality of Life" OR "Quality-Adjusted Life Years" OR "health utility" OR "health utilities" OR productivity OR "EuroQol" OR "standard gamble" OR "time trade off" OR "time trade-off" OR "time tradeoff" OR "TTO" OR "EQ5D" OR "EQ-5D" OR "EQ 5D" OR "EuroQoL 5D" OR "EORTC" OR "health utility index" OR "health utilities index" OR (health AND utilit* AND index) OR "HUI" OR "SF-6D" OR sf6* OR sf 6* OR short form 6* OR shortform 6* OR "sf six" OR "sfsix" OR "shortform six" OR "short form six" OR "QALY" OR "quality adjusted life year" OR "quality-adjusted life years" OR "quality adjusted life-year" OR "quality-adjusted life-year" OR "quality-adjusted life-year" OR "quality of well being" OR "quality of well-being" OR "daly" OR "dalys" OR "disability adjusted life year" OR "disability adjusted life years" OR "SF-36" OR "sf36" OR "sf 36" OR "short form 36" OR "shortform 36" OR "sf thirtysix" OR "sf thirty six" OR "shortform thirtysix" OR "shortform thirty six" OR "short form thirty six" OR "short form thirtysix" OR "short form thirty six" OR "Short Form Health Survey" OR "willingness to pay" OR (utilit* AND score*) OR (utilit* AND weight*) OR "Assessment of Quality of Life" OR "AQOL" OR "quality of life" OR "patient reported outcome" OR "patient reported outcomes" OR satisfaction OR utilities OR disutility OR disutilities OR "functional status" OR "physical function" OR "15D" OR "15-dimensional" OR "15 dimensional" OR "QWB" OR "QWB-SA" OR "quality of well being self-administered" OR "quality of well-being self-administered" OR "quality of well-being-self-administered" OR "quality of well being-self administered")	0
Exclusions		
#6	SU animal* NOT SU human*	180
#7	TI (Comment* OR Letter OR Editorial)	39,851
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7)	0
#9	#8 AND (ZL "english" OR ZL "german" OR ZL "french")	0

First Update - Search Strategy Using the Cochrane Library to Identify Economic Studies of HER2+ Breast Cancer (Conducted on 19 February, 2018)

Search No.	Search Terms	No. of Articles
Disease		
#1	#1 MeSH descriptor: [Breast Neoplasms] explode all trees 10,607 #2 breast next neoplasm* or breast next cancer* or breast next carcinoma* or breast next tumor* or breast next tumour* or mammary next cancer* or mammary next carcinoma* or mammary next neoplasm*:ti,ab,kw (Word variations have been searched) 25,940 #3 #1 or #2 25,948	25,948
Population		
#2	#4 MeSH descriptor: [Receptor, ErbB-2] explode all trees 720 #5 "erbB-2" or erbB2 or "erbB 2" or "human epidermal growth factor receptor 2" or (oncogene and neu) or HER2* or HER next 2*:ti,ab,kw (Word variations have been searched) 6,677 #6 MeSH descriptor: [Chemoradiotherapy, Adjuvant] explode all trees 145 #7 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees 3,942 #8 MeSH descriptor: [Neoadjuvant Therapy] explode all trees 1,078 #9 adjuvant* or neoadjuvant* or neo next adjuvant*:ti,ab,kw (Word variations have been searched)25,259 #10 #3 and (#4 or #5) and (#6 or #7 or #8 or #9) 1,579	1,579
Economic Models		
#3	#11 MeSH descriptor: [Cost-Benefit Analysis] explode all trees 18,672 #12 MeSH descriptor: [Models, Economic] explode all trees 2,039 #13 MeSH descriptor: [Models, Econometric] explode all trees 465 #14 MeSH descriptor: [Costs and Cost Analysis] explode all trees 25,814 #15 MeSH descriptor: [Economics] explode all trees 28,009 #16 MeSH descriptor: [Economics, Hospital] explode all trees 1,803 #17 MeSH descriptor: [Economics, Medical] explode all trees 105 #18 MeSH descriptor: [Economics, Nursing] explode all trees 21 #19 MeSH descriptor: [Economics, Pharmaceutical] explode all trees 244 #20 MeSH descriptor: [Cost Savings] explode all trees 1,028 #21 cost next effective* or modeling or modelling or economic next model* or (model* and (cost or costs or economic* or pharmacoeconomic*)) or Markov or "decision analysis" or "decision-analytic models" or "cost consequence" or ((cost or costs) and (effective* or utilit* or benefit* or minimi*)) or "discrete event simulation" or "cost analysis" or "cost-analysis" or "cost-minimisation analysis" or economic next benefit* or "cost utility" or "cost-utility" or costminimization or costminimisation or "cost-minimization" or "cost-minimisation" or "cost minimization" or "cost minimisation" or "budget impact" or econometric or "economic evaluation":ti,ab,kw (Word variations have been searched) 134,809 #22 #10 and (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21) 354	354
Cost and Resource Use		
#4	#23 MeSH descriptor: [Health Resources] explode all trees and with qualifier(s): [Utilization - UT] 430 #24 MeSH descriptor: [Fees and Charges] explode all trees 515 #25 MeSH descriptor: [Health Care Costs] explode all trees 7,535 #26 MeSH descriptor: [Cost of Illness] explode all trees 1,363 #27 MeSH descriptor: [Health Expenditures] explode all trees 352 #28 MeSH descriptor: [Hospitalization] explode all trees 15,311 #29 MeSH descriptor: [Length of Stay] explode all trees 8,204 #30 MeSH descriptor: [Drug Utilization] explode all trees 605 #31 MeSH descriptor: [Physicians] explode all trees and with qualifier(s): [Economics - EC] 64 #32 MeSH descriptor: [Physicians] explode all trees and with qualifier(s): [Utilization - UT] 26 #33 MeSH descriptor: [General Practitioners] explode all trees and with qualifier(s): [Economics - EC] 4 #34 MeSH descriptor: [General Practitioners] explode all trees and with qualifier(s): [Utilization - UT] 2 #35 MeSH descriptor: [Emergency Treatment] explode all trees and with qualifier(s): [Economics - EC] 132 #36 MeSH descriptor: [Emergency Treatment] explode all trees and with qualifier(s): [Utilization - UT] 46 #37 MeSH descriptor: [Emergency Service, Hospital] explode all trees and with qualifier(s): [Economics - EC] 243	119

Search No.	Search Terms	No. of Articles
	#38 MeSH descriptor: [Emergency Service, Hospital] explode all trees and with qualifier(s): [Utilization - UT] 287 #39 MeSH descriptor: [Absenteeism] explode all trees 535 #40 MeSH descriptor: [Presenteeism] explode all trees 12 #41 MeSH descriptor: [Sick Leave] explode all trees 571 #42 MeSH descriptor: [Return to Work] explode all trees 165 #43 (Economic* and burden*) or economic* or employ* or unemploy* or "resource use" or "resource utilization" or "resource utilisation" or resource next utili* or "health care use" or "health service use" or "health services use" or "health care utilization" or "healthcare utilization" or "health care utilisation" or "healthcare utilisation" or "health resource utilization" or "health resource utilisation" or "health service utilization" or "health service utilisation" or "health services utilization" or "health services utilisation" or pharmacoeconomic* or pharmaco next economic* or "pharmaceutical economics" or price* or pricing or cost or costs or budget* or expenditure* or "health care cost" or "healthcare cost" or "health care costs" or "healthcare costs" or "productivity cost" or "productivity costs" or "societal cost" or "societal costs" or ((direct or indirect) and (cost or costs)) or (medication and (cost or costs)) or (physician and (cost or costs)) or (hospitalization and (cost or costs)) or (hospitalisation and (cost or costs)) or hospitalization or hospitalisation or "hospital visit" or medication or "physician visit" or "GP visit" or "general practitioner visit" or "ED visit" or "emergency department visit" or "emergency room visit" or "ER visit" or absenteeism or presenteeism or "missed work" next day* or "work absence" or "sickness absence" or "sick leave" or "disability leave" or sick next day* or illness next day*:ti,ab,kw (Word variations have been searched) 152,483 #44 #10 and (#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43) 119	
Utility		
#5	#45 MeSH descriptor: [Quality of Life] explode all trees 21,408 #46 MeSH descriptor: [Quality-Adjusted Life Years] explode all trees 4,298 #47 "quality of life" or "health utility" or "health utilities" or productivity or EuroQol or "standard gamble" or "time trade off" or "time trade-off" or "time tradeoff" or TTO or EQ5D or "EQ-5D" or "EQ 5D" or "EuroQoL 5D" or EORTC or "health utility index" or "health utilities index" or (health and utilit* and index) or HUI or "SF-6D" or sf6* or sf next 6* or "short form" next 6* or shortform next 6* or "sf six" or sfsix or "shortform six" or "short form six" or QALY or "quality adjusted life year" or "quality-adjusted life years" or "quality adjusted life-year" or "quality-adjusted life-year" or "quality-adjusted life-year" or "quality of well being" or "quality of well-being" or daly or dalys or "disability adjusted life year" or "disability adjusted life years" or "SF-36" or sf36 or "sf 36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six" or "Short Form Health Survey" or "willingness to pay" or (utilit* and score*) or (utilit* and weight*) or "Assessment of Quality of Life" or AQOL or "patient reported outcome" or "patient reported outcomes" or satisfaction or utilities or disutility or disutilities or "functional status" or "physical function" or 15D or "15-dimensional" or "15 dimensional" or QWB or "QWB-SA" or "quality of well being self-administered" or "quality of well-being self-administered" or "quality of well-being-self-administered" or "quality of well being-self administered":ti,ab,kw (Word variations have been searched) 106,851 #48 #10 and (#45 or #46 or #47) 174	174
Exclusions		
#6	#49 MeSH descriptor: [Animals] explode all trees 8,542 #50 MeSH descriptor: [Humans] explode all trees 202 #51 #49 not #50 8,340	8,340
#7	#52 Comment or Letter or Editorial:pt (Word variations have been searched) 8,926	8,926
Totals		
#9	(#3 OR #4 OR #5) NOT (#6 OR #7) #9 Publication year 2016-2018 Cochrane Reviews - 0 Other Reviews - 0 Trials – 228 Methods Studies -0 Economic Evaluations – 0	518 228

First Update - Search Strategy Using BIOSIS to Identify Economic Studies of HER2+ Breast Cancer (Conducted on 20 February, 2018)

Search No.	Search Terms	No. of Articles
Disease		
#1	ti,ab,su(breast P/0 neoplasm* OR breast P/0 cancer* OR breast P/0 carcinoma* OR breast p/0 tumor* OR breast P/0 tumour* OR mammary P/0 cancer* OR mammary P/0 carcinoma* OR mammary P/0 neoplasm*)	299,808
Population		
#2	#1 AND ti,ab,su("erbB-2" OR erbB2 OR "erbB 2" OR "human epidermal growth factor receptor 2" OR (oncogene AND neu) OR HER2* OR HER P/0 2) AND (su("Chemoradiotherapy Adjuvant" OR "Chemotherapy Adjuvant" OR "Neoadjuvant Therapy") OR ti,ab,su(adjuvant* OR neoadjuvant* OR neo P/0 adjuvant*))	2,933
Economic Models		
#3	#2 AND (su("Cost-Benefit Analysis" OR "Models Economic" OR "Models Econometric" OR "Costs and Cost Analysis" OR Economics OR "Economics Hospital" OR "Economics Medical" OR "Economics Nursing" OR "Economics Pharmaceutical" OR "Cost Savings") OR ti,ab,su(cost P/0 effective* OR modeling OR modelling OR economic P/0 model* OR (model* AND (cost OR costs OR economic* OR pharmacoeconomic*)) OR Markov OR "decision analysis" OR "decision-analytic models" OR "cost consequence" OR ((cost OR costs) AND (effective* OR utilit* OR benefit* OR minimi*)) OR "discrete event simulation" OR "cost analysis" OR "cost-analysis" OR "cost-minimisation analysis" OR economic P/0 benefit* OR "cost utility" OR "cost-utility" OR costminimization OR costminimisation OR "cost-minimization" OR "cost-minimisation" OR "cost minimization" OR "cost minimisation" OR "budget impact" OR econometric OR "economic evaluation"))	79
Cost and Resource Use		
#4	#2 AND (su("Health Resources" P/0 utilization OR Fees P/1 Charges OR "Health Care Costs" OR "Cost of Illness" OR "Health Expenditures" OR Hospitalization OR "Length of Stay" OR "Drug Utilization" OR Physicians P/0 economics OR Physicians P/0 utilization OR "General Practitioners" P/0 economics OR "General Practitioners" P/0 utilization OR "Emergency Treatment" P/0 economics OR "Emergency Treatment" P/0 utilization OR "Emergency Service Hospital" P/0 economics OR "Emergency Service Hospital" P/0 utilization OR Absenteeism OR Presenteeism OR "Sick Leave" OR "Return to Work") OR ti,ab,su("resource use" OR "resource utilization" OR "resource utilisation" OR resource P/0 utili* OR "health care use" OR "health service use" OR "health services use" OR "health care utilization" OR "healthcare utilization" OR "health care utilisation" OR "healthcare utilisation" OR "health resource utilization" OR "health resource utilisation" OR "health service utilization" OR "health service utilisation" OR "health services utilization" OR "health services utilisation" OR pharmacoeconomic* OR pharmaco P/0 economic* OR "pharmaceutical economics" OR price* OR pricing OR cost OR costs OR budget* OR expenditure* OR "health care cost" OR "healthcare cost" OR "health care costs" OR "healthcare costs" OR "productivity cost" OR "productivity costs" OR "societal cost" OR "societal costs" OR ((direct OR indirect) AND (cost OR costs)) OR (medication AND (cost OR costs)) OR (physician AND (cost OR costs)) OR (hospitalization AND (cost OR costs)) OR (hospitalisation AND (cost OR costs)) OR hospitalization OR hospitalisation OR "hospital visit" OR medication OR "physician visit" OR "GP visit" OR "general practitioner visit" OR "ED visit" OR "emergency department visit" OR "emergency room visit" OR "ER visit" OR absenteeism OR presenteeism OR "missed work" P/0 day* OR "work absence" OR "sickness absence" OR "sick leave" OR "disability leave" OR sick P/0 day* OR illness P/0 day*) OR ti((Economic* AND burden*) OR economic* OR employ* OR unemploy*))	88
Utility		
#5	#2 AND (su("Quality of Life" OR "Quality-Adjusted Life Years") OR ti,ab,su("health utility" OR "health utilities" OR productivity OR EuroQol OR "standard gamble" OR "time trade off" OR "time trade-off" OR "time tradeoff" OR TTO OR EQ5D OR "EQ-5D" OR "EQ 5D" OR "EuroQoL 5D" OR EORTC OR "health utility index" OR "health utilities index" OR (health AND utilit* AND index) OR HUI OR "SF-6D" OR sf6* OR sf P/0 6 OR "short form" P/0 6 OR shortform P/0 6 OR "sf six" OR sfsix OR "shortform six" OR "short form six" OR QALY OR "quality adjusted life year" OR "quality-adjusted life years" OR "quality adjusted life-year" OR "quality-adjusted life-year" OR "quality-adjusted life-year" OR "quality of well being" OR "quality of well-being" OR daly OR dalys OR "disability adjusted life year" OR "disability adjusted life years" OR "SF-36" OR sf36 OR "sf 36" OR "short form 36" OR "shortform 36" OR "sf thirtysix" OR "sf thirty six" OR "shortform thirtysix" OR "shortform thirty six" OR "short form thirty six" OR "short form thirtysix" OR "short form thirty six" OR "Short Form Health Survey" OR "willingness to pay" OR (utilit* AND score*) OR (utilit*	111

Search No.	Search Terms	No. of Articles
	AND weight*) OR "Assessment of Quality of Life" OR AQOL OR "patient reported outcome" OR "patient reported outcomes" OR satisfaction OR utilities OR disutility OR disutilities OR "functional status" OR "physical function" OR 15D OR "15-dimensional" OR "15 dimensional" OR QWB OR "QWB-SA" OR "quality of well being self-administered" OR "quality of well-being self-administered" OR "quality of well-being-self-administered" OR "quality of well being-self administered") OR ti("quality of life"))	
Exclusions		
#6	su(animal) NOT su(human)	8,658,597
#7	dtype(Comment* OR Letter OR Editorial)	200,178
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7)	194
#9	#8 AND la(English OR German OR French) Date: From August 09 2016 to February 28 2018	37

Second Update - Search Strategy Using Embase to Identify Economic Studies of HER2+ Breast Cancer (Conducted on 21 November, 2018)

Search No.	Search Terms	No. of Articles
Disease		
#1	'breast tumor'/exp OR (breast NEXT/1 neoplasm*):ti,ab,de OR (breast NEXT/1 cancer*):ti,ab,de OR (breast NEXT/1 carcinoma*):ti,ab,de OR (breast NEXT/1 tumor*):ti,ab,de OR (breast NEXT/1 tumour*):ti,ab,de OR (mammary NEXT/1 cancer*):ti,ab,de OR (mammary NEXT/1 carcinoma*):ti,ab,de OR (mammary NEXT/1 neoplasm*):ti,ab,de	549,922
Population		
#2	#1 AND (('epidermal growth factor receptor 2'/exp/mj OR 'erbB-2':ti,ab,de OR erbB2:ti,ab,de OR 'erbB 2':ti,ab,de OR 'human epidermal growth factor receptor 2':ti,ab,de OR (oncogene:ti,ab,de AND neu:ti,ab,de) OR HER2*:ti,ab,de OR 'HER-2':ti,ab,de OR 'HER 2':ti,ab,de) AND ('adjuvant chemoradiotherapy'/exp OR 'adjuvant chemotherapy'/exp OR 'adjuvant therapy'/exp OR adjuvant*:ti,ab,de OR neoadjuvant*:ti,ab,de OR (neo NEXT/1 adjuvant*):ti,ab,de))	12,689
Economic Models		
#3	#2 AND ('cost benefit analysis'/exp OR 'statistical model'/exp OR 'cost'/exp OR 'economics'/exp OR 'health economics'/exp OR 'pharmacoeconomics'/exp OR 'cost control'/exp OR (cost NEXT/1 effective*):ti,ab,de OR modeling:ti,ab,de OR modelling:ti,ab,de OR (economic NEXT/1 model*):ti,ab,de OR (model*:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de OR economic*:ti,ab,de OR pharmacoeconomic*:ti,ab,de)) OR Markov:ti,ab,de OR 'decision analysis':ti,ab,de OR 'decision-analytic models':ti,ab,de OR 'cost consequence':ti,ab,de OR ((cost:ti,ab,de OR costs:ti,ab,de) AND (effective*:ti,ab,de OR utilit*:ti,ab,de OR benefit*:ti,ab,de OR minimi*:ti,ab,de)) OR 'discrete event simulation':ti,ab,de OR 'cost analysis':ti,ab,de OR 'cost-analysis':ti,ab,de OR 'cost-minimisation analysis':ti,ab,de OR (economic NEXT/1 benefit*):ti,ab,de OR 'cost utility':ti,ab,de OR 'cost-utility':ti,ab,de OR costminimization:ti,ab,de OR costminimisation:ti,ab,de OR 'cost-minimization':ti,ab,de OR 'cost-minimisation':ti,ab,de OR 'cost minimization':ti,ab,de OR 'cost minimisation':ti,ab,de OR 'budget impact':ti,ab,de OR econometric:ti,ab,de OR 'economic evaluation':ti,ab,de)	775
Cost and Resource Use		
#4	#2 AND ('health care utilization'/exp OR 'fee'/exp OR 'health care cost'/exp OR 'cost of illness'/exp OR 'hospitalization'/exp OR 'length of stay'/exp OR 'drug utilization'/exp OR (('physician'/exp OR 'general practitioner'/exp OR 'emergency treatment'/exp OR 'emergency health service'/exp) AND ('health care utilization'/exp OR 'health economics'/exp)) OR 'absenteeism'/exp OR 'presenteeism'/exp OR 'medical leave'/exp OR 'return to work'/exp OR 'resource use':ti,ab,de OR 'resource utilization':ti,ab,de OR 'resource utilisation':ti,ab,de OR (resource NEXT/1 utili*):ti,ab,de OR 'health care use':ti,ab,de OR 'health service use':ti,ab,de OR 'health services use':ti,ab,de OR 'health care utilization':ti,ab,de OR 'healthcare utilization':ti,ab,de OR 'health care utilisation':ti,ab,de OR 'healthcare utilisation':ti,ab,de OR 'health resource utilization':ti,ab,de OR 'health resource utilisation':ti,ab,de OR 'health service utilization':ti,ab,de OR 'health service utilisation':ti,ab,de OR 'health services utilization':ti,ab,de OR 'health services utilisation':ti,ab,de OR (Economic*:ti AND burden*:ti) OR economic*:ti OR pharmacoeconomic*:ti,ab,de OR (pharmaco NEXT/1 economic*):ti,ab,de OR 'pharmaceutical economics':ti,ab,de OR price*:ti,ab,de OR pricing:ti,ab,de OR cost:ti,ab,de OR costs:ti,ab,de OR budget*:ti,ab,de OR expenditure*:ti,ab,de OR 'health care cost':ti,ab,de OR 'healthcare cost':ti,ab,de OR 'health care costs':ti,ab,de OR 'healthcare costs':ti,ab,de OR 'productivity	687

Search No.	Search Terms	No. of Articles
	cost':ti,ab,de OR 'productivity costs':ti,ab,de OR 'societal cost':ti,ab,de OR 'societal costs':ti,ab,de OR ((direct:ti,ab,de OR indirect:ti,ab,de) AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (medication:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (physician:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (hospitalization:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR (hospitalisation:ti,ab,de AND (cost:ti,ab,de OR costs:ti,ab,de)) OR hospitalization:ti,ab,de OR hospitalisation:ti,ab,de OR 'hospital visit':ti,ab,de OR medication:ti,ab,de OR 'physician visit':ti,ab,de OR 'GP visit':ti,ab,de OR 'general practitioner visit':ti,ab,de OR 'ED visit':ti,ab,de OR 'emergency department visit':ti,ab,de OR 'emergency room visit':ti,ab,de OR 'ER visit':ti,ab,de OR employ*:ti OR unemploy*:ti OR absenteeism:ti,ab,de OR presenteeism:ti,ab,de OR ('missed work' NEXT/1 day*):ti,ab,de OR 'work absence':ti,ab,de OR 'sickness absence':ti,ab,de OR 'sick leave':ti,ab,de OR 'disability leave':ti,ab,de OR (sick NEXT/1 day*):ti,ab,de OR (illness NEXT/1 day*):ti,ab,de)	
Utility		
#5	#2 AND ('quality of life'/exp OR 'quality adjusted life year'/exp OR 'health utility':ti,ab,de OR 'health utilities':ti,ab,de OR productivity:ti,ab,de OR EuroQol:ti,ab,de OR 'standard gamble':ti,ab,de OR 'time trade off':ti,ab,de OR 'time trade-off':ti,ab,de OR 'time tradeoff':ti,ab,de OR TTO:ti,ab,de OR EQ5D:ti,ab,de OR 'EQ-5D':ti,ab,de OR 'EQ 5D':ti,ab,de OR 'EuroQoL 5D':ti,ab,de OR EORTC:ti,ab,de OR 'health utility index':ti,ab,de OR 'health utilities index':ti,ab,de OR (health:ti,ab,de AND utilit*:ti,ab,de AND index:ti,ab,de) OR HUI:ti,ab,de OR 'SF-6D':ti,ab,de OR sf6*:ti,ab,de OR 'sf 6':ti,ab,de OR 'short form 6':ti,ab,de OR 'shortform 6':ti,ab,de OR 'sf six':ti,ab,de OR sfsix:ti,ab,de OR 'shortform six':ti,ab,de OR 'short form six':ti,ab,de OR QALY:ti,ab,de OR 'quality adjusted life year':ti,ab,de OR 'quality-adjusted life years':ti,ab,de OR 'quality adjusted life-year':ti,ab,de OR 'quality-adjusted life-year':ti,ab,de OR 'quality-adjusted life-year':ti,ab,de OR 'quality of well being':ti,ab,de OR 'quality of well-being':ti,ab,de OR daly:ti,ab,de OR dalys:ti,ab,de OR 'disability adjusted life year':ti,ab,de OR 'disability adjusted life years':ti,ab,de OR 'SF-36':ti,ab,de OR sf36:ti,ab,de OR 'sf 36':ti,ab,de OR 'short form 36':ti,ab,de OR 'shortform 36':ti,ab,de OR 'sf thirtysix':ti,ab,de OR 'sf thirty six':ti,ab,de OR 'shortform thirtysix':ti,ab,de OR 'shortform thirty six':ti,ab,de OR 'short form thirty six':ti,ab,de OR 'short form thirtysix':ti,ab,de OR 'short form thirty six':ti,ab,de OR 'Short Form Health Survey':ti,ab,de OR 'willingness to pay':ti,ab,de OR (utilit*:ti,ab,de AND score*:ti,ab,de) OR (utilit*:ti,ab,de AND weight*:ti,ab,de) OR 'Assessment of Quality of Life':ti,ab,de OR AQOL:ti,ab,de OR 'quality of life':ti OR 'patient reported outcome':ti,ab,de OR 'patient reported outcomes':ti,ab,de OR satisfaction:ti,ab,de OR utilities:ti,ab,de OR disutility:ti,ab,de OR disutilities:ti,ab,de OR 'functional status':ti,ab,de OR 'physical function':ti,ab,de OR 15D:ti,ab,de OR '15-dimensional':ti,ab,de OR '15 dimensional':ti,ab,de OR QWB:ti,ab,de OR 'QWB-SA':ti,ab,de OR 'quality of well being self-administered':ti,ab,de OR 'quality of well-being self-administered':ti,ab,de OR 'quality of well-being-self-administered':ti,ab,de OR 'quality of well being-self administered':ti,ab,de)	644
Exclusions		
#6	'animal'/exp NOT 'human'/exp	5,149,336
#7	Comment*:ti OR Letter:it OR Editorial:it OR 'conference paper':it OR 'conference abstract':it	5,683,426
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7)	657
#9	#8 AND ([english]/lim OR [german]/lim OR [french]/lim)	635
#10	#8 AND ([english]/lim OR [german]/lim OR [french]/lim) AND [19-10-2016]/sd NOT [28-02-2018]/sd	80

Second Update - Search Strategy Using EconLit to Identify Economic Studies of HER2+ Breast Cancer (Conducted on 21 November, 2018)

Search No.	Search Terms	No. of Articles
Disease		
#1	"breast neoplasm*" OR "breast cancer*" OR "breast carcinoma*" OR "breast tumor*" OR "breast tumour*" OR "mammary cancer*" OR "mammary carcinoma*" OR "mammary neoplasm*"	261
Population		
#2	#1 AND (("ErbB-2 Receptor" OR "erbB-2" OR erbB2 OR "erbB 2" OR "human epidermal growth factor receptor 2" OR (oncogene AND neu) OR "HER2*" OR "HER-2*" OR "HER 2*") AND ("Adjuvant Chemoradiotherapy" OR "Adjuvant Chemotherapy" OR "Neoadjuvant Therapy" OR adjuvant* OR neoadjuvant* OR "neo-adjuvant*"))	0

Search No.	Search Terms	No. of Articles
Economic Models		
#3	#2 AND (“Cost-Benefit Analysis” OR “Models, Economic” OR “Models, Econometric” OR “Costs and Cost Analysis” OR “Economics” OR “Economics, Hospital” OR “Economics, Medical” OR “Economics, Nursing” OR “Economics, Pharmaceutical” OR “Cost Savings” OR cost effective* OR cost-effective* OR modeling OR modelling OR economic model* OR (model* AND (cost OR costs OR economic* OR pharmacoeconomic*)) OR Markov OR “decision analysis” OR “decision-analytic models” OR “cost consequence” OR ((cost OR costs) AND (effective* OR utilit* OR benefit* OR minimi*)) OR “discrete event simulation” OR “cost analysis” OR “cost-analysis” OR “cost-minimisation analysis” OR economic benefit* OR “cost utility” OR “cost-utility” OR costminimization OR costminimisation OR “cost-minimization” OR “cost-minimisation” OR “cost minimization” OR “cost minimisation” OR “budget impact” OR econometric OR “economic evaluation”)	0
Cost and Resource Use		
#4	#2 AND (“Health Resources/utilization” OR “Fees and Charges” OR “Health Care Costs” OR “Cost of Illness” OR “Health Expenditures” OR “Hospitalization” OR “Length of Stay” OR “Drug Utilization” OR “Physicians/economics” OR “Physicians/utilization” OR “General Practitioners/economics” OR “General Practitioners/utilization” OR “Emergency Treatment/economics” OR “Emergency Treatment/utilization” OR “Emergency Service, Hospital/economics” OR “Emergency Service, Hospital/utilization” OR “Absenteeism” OR “Presenteeism” OR “Sick Leave” OR “Return to Work” OR “resource use” OR “resource utilization” OR “resource utilisation” OR resource utili* OR “health care use” OR “health service use” OR “health services use” OR “health care utilization” OR “healthcare utilization” OR “health care utilisation” OR “healthcare utilisation” OR “health resource utilization” OR “health resource utilisation” OR “health service utilization” OR “health service utilisation” OR “health services utilization” OR “health services utilisation” OR (Economic* AND burden*) OR economic* OR pharmacoeconomic* OR pharmaco economic* OR “pharmaceutical economics” OR price* OR pricing OR cost OR costs OR budget* OR expenditure* OR “health care cost” OR “healthcare cost” OR “health care costs” OR “healthcare costs” OR “productivity cost” OR “productivity costs” OR “societal cost” OR “societal costs” OR ((direct OR indirect) AND (cost OR costs)) OR (medication AND (cost OR costs)) OR (physician AND (cost OR costs)) OR (hospitalization AND (cost OR costs)) OR (hospitalisation AND (cost OR costs)) OR hospitalization OR hospitalisation OR “hospital visit” OR medication OR “physician visit” OR “GP visit” OR “general practitioner visit” OR “ED visit” OR “emergency department visit” OR “emergency room visit” OR “ER visit” OR employ* OR unemploy* OR absenteeism OR presenteeism OR missed work day* OR “work absence” OR “sickness absence” OR “sick leave” OR “disability leave” OR sick day* OR illness day*)	0
Utility		
#5	#2 AND (“Quality of Life” OR “Quality-Adjusted Life Years” OR “health utility” OR “health utilities” OR productivity OR “EuroQol” OR “standard gamble” OR “time trade off” OR “time trade-off” OR “time tradeoff” OR “TTO” OR “EQ5D” OR “EQ-5D” OR “EQ 5D” OR “EuroQoL 5D” OR “EORTC” OR “health utility index” OR “health utilities index” OR (health AND utilit* AND index) OR “HUI” OR “SF-6D” OR sf6* OR sf 6* OR short form 6* OR shortform 6* OR “sf six” OR “sfsix” OR “shortform six” OR “short form six” OR “QALY” OR “quality adjusted life year” OR “quality-adjusted life years” OR “quality adjusted life-year” OR “quality-adjusted life-year” OR “quality-adjusted life-year” OR “quality of well being” OR “quality of well-being” OR “daly” OR “dalys” OR “disability adjusted life year” OR “disability adjusted life years” OR “SF-36” OR “sf36” OR “sf 36” OR “short form 36” OR “shortform 36” OR “sf thirtysix” OR “sf thirty six” OR “shortform thirtysix” OR “shortform thirty six” OR “short form thirty six” OR “short form thirtysix” OR “short form thirty six” OR “Short Form Health Survey” OR “willingness to pay” OR (utilit* AND score*) OR (utilit* AND weight*) OR “Assessment of Quality of Life” OR “AQOL” OR “quality of life” OR “patient reported outcome” OR “patient reported outcomes” OR satisfaction OR utilities OR disutility OR disutilities OR “functional status” OR “physical function” OR “15D” OR “15-dimensional” OR “15 dimensional” OR “QWB” OR “QWB-SA” OR “quality of well being self-administered” OR “quality of well-being self-administered” OR “quality of well-being-self-administered” OR “quality of well being-self administered”)	0
Exclusions		
#6	SU animal* NOT SU human*	193
#7	TI (Comment* OR Letter OR Editorial)	40,451
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7)	0
#9	#8 AND (ZL "english" OR ZL "german" OR ZL "french")	0

Second Update - Search Strategy Using the Cochrane Library to Identify Economic Studies of HER2+ Breast Cancer (Conducted on 21 November, 2018)

Search No.	Search Terms	No. of Articles
Disease		
#1	#1 MeSH descriptor: [Breast Neoplasms] explode all trees 11,147 #2 breast next neoplasm* or breast next cancer* or breast next carcinoma* or breast next tumor* or breast next tumour* or mammary next cancer* or mammary next carcinoma* or mammary next neoplasm*:ti,ab,kw (Word variations have been searched) 26,552 #3 #1 or #2 26,564	26,564
Population		
#2	#4 MeSH descriptor: [Receptor, ErbB-2] explode all trees 641 #5 "erbB-2" or erbB2 or "erbB 2" or "human epidermal growth factor receptor 2" or (oncogene and neu) or HER2* or HER next 2*:ti,ab,kw (Word variations have been searched) 5,188 #6 MeSH descriptor: [Chemoradiotherapy, Adjuvant] explode all trees 133 #7 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees 3,521 #8 MeSH descriptor: [Neoadjuvant Therapy] explode all trees 984 #9 adjuvant* or neoadjuvant* or neo next adjuvant*:ti,ab,kw (Word variations have been searched)27,129 #10 #3 and (#4 or #5) and (#6 or #7 or #8 or #9) 1,786	1,786
Economic Models		
#3	#11 MeSH descriptor: [Cost-Benefit Analysis] explode all trees 6,210 #12 MeSH descriptor: [Models, Economic] explode all trees 299 #13 MeSH descriptor: [Models, Econometric] explode all trees 80 #14 MeSH descriptor: [Costs and Cost Analysis] explode all trees 9,552 #15 MeSH descriptor: [Economics] explode all trees 11,384 #16 MeSH descriptor: [Economics, Hospital] explode all trees 661 #17 MeSH descriptor: [Economics, Medical] explode all trees 61 #18 MeSH descriptor: [Economics, Nursing] explode all trees 12 #19 MeSH descriptor: [Economics, Pharmaceutical] explode all trees 244 #20 MeSH descriptor: [Cost Savings] explode all trees 403 #21 cost next effective* or modeling or modelling or economic next model* or (model* and (cost or costs or economic* or pharmacoeconomic*)) or Markov or "decision analysis" or "decision-analytic models" or "cost consequence" or ((cost or costs) and (effective* or utilit* or benefit* or minimi*)) or "discrete event simulation" or "cost analysis" or "cost-analysis" or "cost-minimisation analysis" or economic next benefit* or "cost utility" or "cost-utility" or costminimization or costminimisation or "cost-minimization" or "cost-minimisation" or "cost minimization" or "cost minimisation" or "budget impact" or econometric or "economic evaluation":ti,ab,kw (Word variations have been searched) 130,946 #22 #10 and (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21) 371	371
Cost and Resource Use		
#4	#23 MeSH descriptor: [Health Resources] explode all trees and with qualifier(s): [Utilization - UT] 262 #24 MeSH descriptor: [Fees and Charges] explode all trees 248 #25 MeSH descriptor: [Health Care Costs] explode all trees 3,196 #26 MeSH descriptor: [Cost of Illness] explode all trees 774 #27 MeSH descriptor: [Health Expenditures] explode all trees 180 #28 MeSH descriptor: [Hospitalization] explode all trees 12,595 #29 MeSH descriptor: [Length of Stay] explode all trees 6,557 #30 MeSH descriptor: [Drug Utilization] explode all trees 483 #31 MeSH descriptor: [Physicians] explode all trees and with qualifier(s): [Economics - EC] 34 #32 MeSH descriptor: [Physicians] explode all trees and with qualifier(s): [Utilization - UT] 23 #33 MeSH descriptor: [General Practitioners] explode all trees and with qualifier(s): [Economics - EC] 4 #34 MeSH descriptor: [General Practitioners] explode all trees and with qualifier(s): [Utilization - UT] 2 #35 MeSH descriptor: [Emergency Treatment] explode all trees and with qualifier(s): [Economics - EC] 60 #36 MeSH descriptor: [Emergency Treatment] explode all trees and with qualifier(s): [Utilization - UT] 40	219

Search No.	Search Terms	No. of Articles
	#37 MeSH descriptor: [Emergency Service, Hospital] explode all trees and with qualifier(s): [Economics - EC] 100 #38 MeSH descriptor: [Emergency Service, Hospital] explode all trees and with qualifier(s): [Utilization - UT] 245 #39 MeSH descriptor: [Absenteeism] explode all trees 462 #40 MeSH descriptor: [Presenteeism] explode all trees 16 #41 MeSH descriptor: [Sick Leave] explode all trees 518 #42 MeSH descriptor: [Return to Work] explode all trees 186 #43 (Economic* and burden*) or economic* or employ* or unemploy* or "resource use" or "resource utilization" or "resource utilisation" or resource next utili* or "health care use" or "health service use" or "health services use" or "health care utilization" or "healthcare utilization" or "health care utilisation" or "healthcare utilisation" or "health resource utilization" or "health resource utilisation" or "health service utilization" or "health service utilisation" or "health services utilization" or "health services utilisation" or pharmacoeconomic* or pharmaco next economic* or "pharmaceutical economics" or price* or pricing or cost or costs or budget* or expenditure* or "health care cost" or "healthcare cost" or "health care costs" or "healthcare costs" or "productivity cost" or "productivity costs" or "societal cost" or "societal costs" or ((direct or indirect) and (cost or costs)) or (medication and (cost or costs)) or (physician and (cost or costs)) or (hospitalization and (cost or costs)) or (hospitalisation and (cost or costs)) or hospitalization or hospitalisation or "hospital visit" or medication or "physician visit" or "GP visit" or "general practitioner visit" or "ED visit" or "emergency department visit" or "emergency room visit" or "ER visit" or absenteeism or presenteeism or "missed work" next day* or "work absence" or "sickness absence" or "sick leave" or "disability leave" or sick next day* or illness next day*:ti,ab,kw (Word variations have been searched) 287,519 #44 #10 and (#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43) 219	
Utility		
#5	#45 MeSH descriptor: [Quality of Life] explode all trees 20,557 #46 MeSH descriptor: [Quality-Adjusted Life Years] explode all trees 1,042 #47 "quality of life" or "health utility" or "health utilities" or productivity or EuroQol or "standard gamble" or "time trade off" or "time trade-off" or "time tradeoff" or TTO or EQ5D or "EQ-5D" or "EQ 5D" or "EuroQoL 5D" or EORTC or "health utility index" or "health utilities index" or (health and utilit* and index) or HUI or "SF-6D" or sf6* or sf next 6* or "short form" next 6* or shortform next 6* or "sf six" or sfsix or "shortform six" or "short form six" or QALY or "quality adjusted life year" or "quality-adjusted life years" or "quality adjusted life-year" or "quality-adjusted life-year" or "quality-adjusted life-year" or "quality of well being" or "quality of well-being" or daly or dalys or "disability adjusted life year" or "disability adjusted life years" or "SF-36" or sf36 or "sf 36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six" or "Short Form Health Survey" or "willingness to pay" or (utilit* and score*) or (utilit* and weight*) or "Assessment of Quality of Life" or AQOL or "patient reported outcome" or "patient reported outcomes" or satisfaction or utilities or disutility or disutilities or "functional status" or "physical function" or 15D or "15-dimensional" or "15 dimensional" or QWB or "QWB-SA" or "quality of well being self-administered" or "quality of well-being self-administered" or "quality of well-being-self-administered" or "quality of well being-self administered":ti,ab,kw (Word variations have been searched) 178,401 #48 #10 and (#45 or #46 or #47) 231	231
Exclusions		
#6	#49 MeSH descriptor: [Animals] explode all trees 16,487 #50 MeSH descriptor: [Humans] explode all trees 8,465 #51 #49 not #50 8,022	8,022
#7	#52 Comment or Letter or Editorial:pt (Word variations have been searched) 9,189	8,926
Totals		
#9	(#3 OR #4 OR #5) NOT (#6 OR #7) #9 Pubication year 2016-2018 Cochrane Reviews - 0 Other Reviews - 0 Trials – 115 (Published 2017-2018) Methods Studies -0 Economic Evaluations – 0	655 145

Second Update- Search Strategy Using BIOSIS to Identify Economic Studies of HER2+ Breast Cancer (Conducted on 21 November, 2018)

Search No.	Search Terms	No. of Articles
Disease		
#1	ti,ab,su(breast P/0 neoplasm* OR breast P/0 cancer* OR breast P/0 carcinoma* OR breast p/0 tumor* OR breast P/0 tumour* OR mammary P/0 cancer* OR mammary P/0 carcinoma* OR mammary P/0 neoplasm*)	314,447
Population		
#2	#1 AND ti,ab,su("erbB-2" OR erbB2 OR "erbB 2" OR "human epidermal growth factor receptor 2" OR (oncogene AND neu) OR HER2* OR HER P/0 2) AND (su("Chemoradiotherapy Adjuvant" OR "Chemotherapy Adjuvant" OR "Neoadjuvant Therapy") OR ti,ab,su(adjuvant* OR neoadjuvant* OR neo P/0 adjuvant*))	3,196
Economic Models		
#3	#2 AND (su("Cost-Benefit Analysis" OR "Models Economic" OR "Models Econometric" OR "Costs and Cost Analysis" OR Economics OR "Economics Hospital" OR "Economics Medical" OR "Economics Nursing" OR "Economics Pharmaceutical" OR "Cost Savings") OR ti,ab,su(cost P/0 effective* OR modeling OR modelling OR economic P/0 model* OR (model* AND (cost OR costs OR economic* OR pharmacoeconomic*)) OR Markov OR "decision analysis" OR "decision-analytic models" OR "cost consequence" OR ((cost OR costs) AND (effective* OR utilit* OR benefit* OR minimi*)) OR "discrete event simulation" OR "cost analysis" OR "cost-analysis" OR "cost-minimisation analysis" OR economic P/0 benefit* OR "cost utility" OR "cost-utility" OR costminimization OR costminimisation OR "cost-minimization" OR "cost-minimisation" OR "cost minimization" OR "cost minimisation" OR "budget impact" OR econometric OR "economic evaluation"))	88
Cost and Resource Use		
#4	#2 AND (su("Health Resources" P/0 utilization OR Fees P/1 Charges OR "Health Care Costs" OR "Cost of Illness" OR "Health Expenditures" OR Hospitalization OR "Length of Stay" OR "Drug Utilization" OR Physicians P/0 economics OR Physicians P/0 utilization OR "General Practitioners" P/0 economics OR "General Practitioners" P/0 utilization OR "Emergency Treatment" P/0 economics OR "Emergency Treatment" P/0 utilization OR "Emergency Service Hospital" P/0 economics OR "Emergency Service Hospital" P/0 utilization OR Absenteeism OR Presenteeism OR "Sick Leave" OR "Return to Work") OR ti,ab,su("resource use" OR "resource utilization" OR "resource utilisation" OR resource P/0 utili* OR "health care use" OR "health service use" OR "health services use" OR "health care utilization" OR "healthcare utilization" OR "health care utilisation" OR "healthcare utilisation" OR "health resource utilization" OR "health resource utilisation" OR "health service utilization" OR "health service utilisation" OR "health services utilization" OR "health services utilisation" OR pharmacoeconomic* OR pharmaco P/0 economic* OR "pharmaceutical economics" OR price* OR pricing OR cost OR costs OR budget* OR expenditure* OR "health care cost" OR "healthcare cost" OR "health care costs" OR "healthcare costs" OR "productivity cost" OR "productivity costs" OR "societal cost" OR "societal costs" OR ((direct OR indirect) AND (cost OR costs)) OR (medication AND (cost OR costs)) OR (physician AND (cost OR costs)) OR (hospitalization AND (cost OR costs)) OR (hospitalisation AND (cost OR costs)) OR hospitalization OR hospitalisation OR "hospital visit" OR medication OR "physician visit" OR "GP visit" OR "general practitioner visit" OR "ED visit" OR "emergency department visit" OR "emergency room visit" OR "ER visit" OR absenteeism OR presenteeism OR "missed work" P/0 day* OR "work absence" OR "sickness absence" OR "sick leave" OR "disability leave" OR sick P/0 day* OR illness P/0 day*) OR ti((Economic* AND burden*) OR economic* OR employ* OR unemploy*))	89
Utility		
#5	#2 AND (su("Quality of Life" OR "Quality-Adjusted Life Years") OR ti,ab,su("health utility" OR "health utilities" OR productivity OR EuroQol OR "standard gamble" OR "time trade off" OR "time trade-off" OR "time tradeoff" OR TTO OR EQ5D OR "EQ-5D" OR "EQ 5D" OR "EuroQoL 5D" OR EORTC OR "health utility index" OR "health utilities index" OR (health AND utilit* AND index) OR HUI OR "SF-6D" OR sf6* OR sf P/0 6 OR "short form" P/0 6 OR shortform P/0 6 OR "sf six" OR sfsix OR "shortform six" OR "short form six" OR QALY OR "quality adjusted life year" OR "quality-adjusted life years" OR "quality adjusted life-year" OR "quality-adjusted life-year" OR "quality-adjusted life-year" OR "quality of well being" OR "quality of well-being" OR daly OR dalys OR "disability adjusted life year" OR "disability adjusted life years" OR "SF-36" OR sf36 OR "sf 36" OR "short form 36" OR "shortform 36" OR "sf thirtysix" OR "sf thirty six" OR "shortform thirtysix" OR "shortform thirty six" OR "short form thirty six" OR "short form thirtysix" OR "short form thirty	123

Search No.	Search Terms	No. of Articles
	six" OR "Short Form Health Survey" OR "willingness to pay" OR (utilit* AND score*) OR (utilit* AND weight*) OR "Assessment of Quality of Life" OR AQOL OR "patient reported outcome" OR "patient reported outcomes" OR satisfaction OR utilities OR disutility OR disutilities OR "functional status" OR "physical function" OR 15D OR "15-dimensional" OR "15 dimensional" OR QWB OR "QWB-SA" OR "quality of well being self-administered" OR "quality of well-being self-administered" OR "quality of well-being-self-administered" OR "quality of well being-self administered") OR ti("quality of life"))	
Exclusions		
#6	su(animal) NOT su(human)	8,822,113
#7	dtype(Comment* OR Letter OR Editorial)	209,104
Totals		
#8	(#3 OR #4 OR #5) NOT (#6 OR #7)	215
#9	#8 AND la(English OR German OR French) Date: From 19 December 2017 to 30 November 2018	23

A2. Please clarify why lines #3 and #5 of the Embase searches do not retrieve the same number of records in Tables 2 and 3 (Appendix D; pages 17 and 18). The numbers found for both the main search and the conference materials search should be the same in these lines of the strategy.

The search strings used in the two searches were identical and they were run on the same day, we therefore assume the slightly higher number of hits in Table 2 versus Table 3 reflects updates to Embase that occurred during the day.

A3. Please provide the missing footnotes from the clinical effectiveness search strategies (Appendix D; pages 18, 19 and 21).

This is an editing error; the footnotes should not have been included.

A4. Please confirm which host was used for the Cochrane Library searches (clinical and cost-effectiveness searches).

The Cochrane Library was searched through the website: https://www.cochranelibrary.com/advanced-search?q=&t=1

A5. Please provide the strategies/search terms used in the clinical effectiveness trials register searches (Appendix D).

The following search terms were used for the electronic searches of clinical trial registries.

Summary of Search Terms and Results of Searches of Clinical Trial Registries

Register Searched; URL	Date of Search	Search Terms Used	Total Number of Trials Identified in Initial Search	Total Number of Trials Potentially Relevant	Number of Relevant Trials
Clinicaltrials. Gov https://clinicaltrials.gov/ct2/search/advanced?cond=&term=&cntry=&state=&city=&dist=	28/11/18	neratinib OR trastuzumab OR pertuzumab OR lapatinib OR trastuzumab emtansine | Interventional Studies | HER2-positive Breast Cancer | Adult, Older Adult	415	79	1
International Clinical Trials Registry Platform Search Portal (World Health Organization) http://apps.who.int/trialsearch/Default.aspx	05/12/18	"early breast cancer" AND HER2 AND (neratinib OR nerlynx OR trastuzumab OR Kadcyla OR herceptin OR pertuzumab OR perjeta OR lapatinib OR tykerb OR tyverb)	22	4	0
European Union's Clinical Trials Register https://www.clinicaltrialsregister.eu/ctr-search/search	05/12/18	HER2 AND positive AND breast AND (neratinib OR nerlynx OR trastuzumab OR Kadcyla OR herceptin OR pertuzumab OR perjeta OR lapatinib OR tykerb OR tyverb)	192	14	0
Germany's Klinische Prufungen PharmNet.Bund https://portal.dimdi.de/clinical-rials/servlet/FlowController/AcceptDisclaimer# DEFANCHOR	06/12/18	Suche nach: brustkrebs [in Title]	23	0	0

General

A6. Priority question: NICE has recommended pertuzumab as a possible treatment before surgery for people with HER2-postive breast cancer that is locally advanced, inflammatory, or in early stage with high risk of re-occurrence (TA424).

a. Given that pertuzumab targets the same receptors as neratinib, please explain what the implications are for the effectiveness of neratinib.

b. Please also amend Figure 1 of document B of the company submission (CS) to show how pertuzumab fits in the treatment pathway.

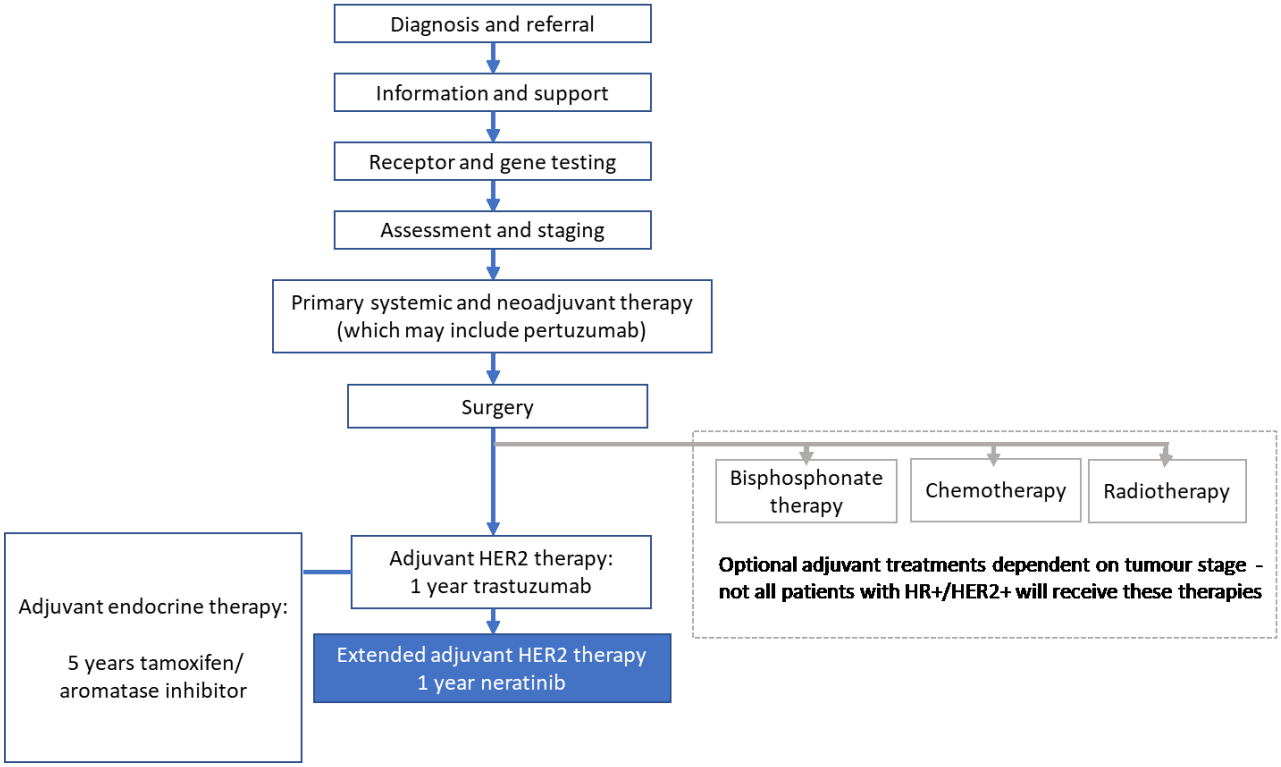
a. Treatments in the neoadjuvant setting are outside the scope of this appraisal. Although pertuzumab and neratinib both target HER2, their modes of action are different. Pertuzumab is an intravenous biological therapy that targets the extracellular domains of HER2 via antibody-dependent, cell-mediated cytotoxicity. Neratinib is an oral, small molecule tyrosine kinase inhibitor that binds irreversibly to

the intracellular domains of EGFR, HER2, and HER4, or their active heterodimers with HER3, simultaneously blocking their downstream signalling pathways.

In ExteNET, prior therapy with HER1 and/or HER2 therapy other than trastuzumab was not permitted, so no patients in this trial should have received neoadjuvant pertuzumab according to the protocol. In CONTROL, neoadjuvant pertuzumab was permitted and 40.1% of patients in the loperamide cohort, 60.9% of patients in the loperamide plus budesonide cohort, and 62.5% in the loperamide plus colestipol cohort had received neoadjuvant pertuzumab.

In current practice, patients in the UK with early breast cancer may receive neoadjuvant pertuzumab if they have early breast cancer that is at high risk of recurrence, or is locally advanced, or inflammatory prior to surgery. If these patients are also HER2+/ HR+ and then complete an adjuvant course of trastuzumab after surgery, they may also be eligible to receive extended adjuvant treatment with neratinib. The addition of neratinib following on from any adjuvant therapy with trastuzumab (and neoadjuvant therapy with pertuzumab) is expected to offer additional efficacy in the extended adjuvant setting on top of the benefit provided by previous trastuzumab-based therapy, as currently there is no further HER2-directed therapy beyond one year of trastuzumab.

b. **Updated Figure 1. Neratinib: Place in Treatment Pathway for Early HR+/HER2+ Breast Cancer**



Abbreviations: HER2+, human epidermal growth factor receptor 2-positive; HR+, hormone receptor-positive.

Note: Following surgery, most patients with HR+/HER2+ breast cancer will receive adjuvant trastuzumab and endocrine therapy, with the options of bisphosphonate, chemotherapy, and radiotherapy dependent on tumour stage and clinical judgement.

Adapted from NICE (2018)

A7. The clinical pathway (Figure 1 in document B in the CS) shows adjuvant endocrine therapy as an alternative to adjuvant HER2 therapy, however, these treatments are permitted to be concurrent. Please amend Figure 1 appropriately to clarify this (see also question A15 and B22).

See response to Question A6b.

A8. The ERG is aware that a technology appraisal for pertuzumab for adjuvant therapy of early HER2-postive breast cancer is in development (ID1192). Please explain what the implications will be for neratinib, if pertuzumab would be recommended.

Pertuzumab in the adjuvant setting was not available through the NHS during the scoping of the neratinib appraisal, so adjuvant pertuzumab has not been considered in the submission.

Pertuzumab and trastuzumab are both HER2-directed therapies that are given concurrently for 1 year following surgery. Although pertuzumab and neratinib both target HER2, their modes of action are different. Pertuzumab is an intravenous biological therapy that targets the extracellular domains of HER2 via antibody-dependent, cell-mediated cytotoxicity. Neratinib is an oral, small molecule tyrosine kinase inhibitor that binds irreversibly to the intracellular domains of EGFR, HER2, and HER4, or their active heterodimers with HER3, simultaneously blocking their downstream signalling pathways.

In ID1192, adjuvant pertuzumab added to trastuzumab has been recommended in patients with HER2+ early stage breast cancer with node-positive disease, regardless of hormone receptor (HR) status. In HR+/HER2+ patients, there is still an unmet need after adjuvant pertuzumab and trastuzumab-based therapy, as 3-year invasive disease-free survival (iDFS) rates from the APHINITY trial only show an absolute benefit of +0.4% (hazard ratio, 0.86; 95% CI, 0.66-1.13; *P* = 0.28) with pertuzumab in patients with HR+ disease, with greater efficacy of +1.6% in HR- disease (von Minckwitz et al., 2017). The addition of neratinib following on from any adjuvant therapy with trastuzumab and pertuzumab is likely to provide additional efficacy in the extended adjuvant setting on top of any provided by adjuvant pertuzumab, as currently there is no further HER2-directed therapy beyond 1 year of trastuzumab and pertuzumab, particularly in HR+ disease.

The use of neratinib in the extended adjuvant setting may be of additional benefit to patients with HR+ disease who will also be taking endocrine therapy in this setting for 5 or more years. Neratinib's intracellular mode of action simultaneously blocks multiple ErbB receptors, and has demonstrated inhibition of bidirectional crosstalk between HER2 and oestrogen receptors (ER) that contributes to drug resistance to both HER2-directed agents and endocrine therapy, something that has not been shown with trastuzumab-based regimens. As pertuzumab only targets the extracellular domain of HER2 via antibody-dependent, cell-mediated cytotoxicity, adjuvant pertuzumab is unlikely to influence the bidirectional crosstalk of the

ER/HER2 signalling pathway and impact any potential resistance to endocrine therapy.

A9. Given that diarrhoea is a common adverse event of neratinib, for which medication is administered orally, please comment on any impact on the absorption as well as the intended clinical effectiveness.

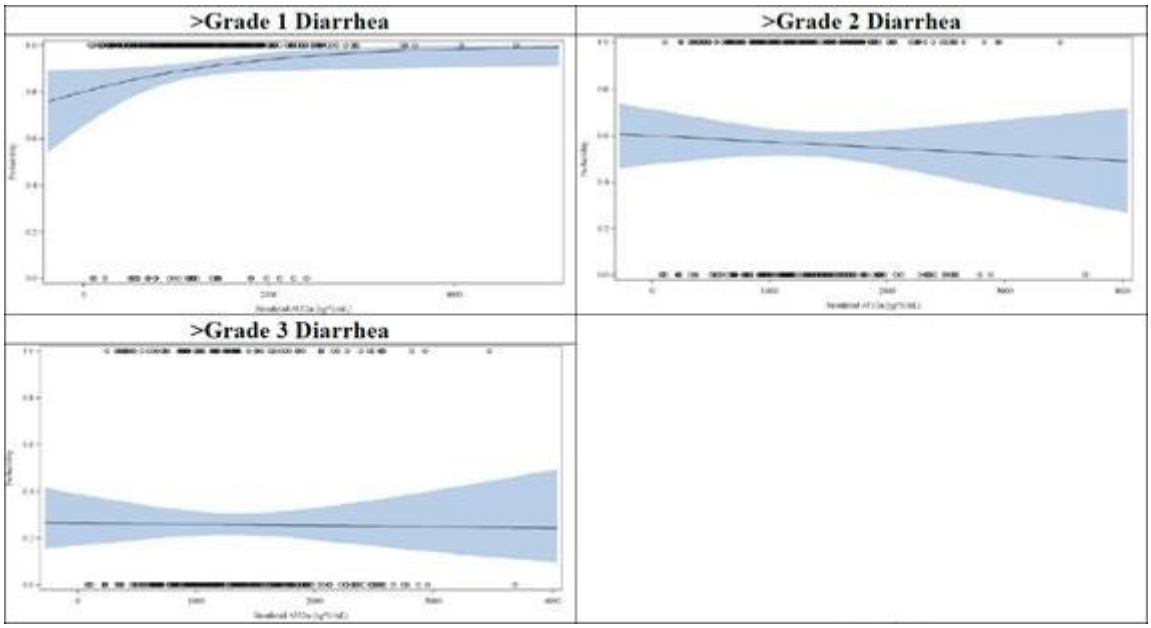
According to the Food and Drug Administration review of neratinib, incidence of diarrhoea (grade 1, 2, or 3) had little effect on pharmacokinetic parameters of neratinib and is not expected to have any effect on absorption or intended clinical effectiveness (see Table). According to Process Performance (PPK) analysis, mandatory use of antidiarrhoea treatment is expected to minimise any grade diarrhoea events and increase bioavailability by approximately 10% at most (assuming no drug-drug interaction between neratinib and the antidiarrhoea drug).

Analysis of Safety Endpoints and Steady State Exposures Adjusted by Average Daily Dose of Neratinib (Neratinib Arm in Studies A1-102, A1-104, A1-201, and A2-3003)

	$C_{trough,ss}$ (ng/mL)		AUC_{ss} (ng*h/mL)		$C_{max,ss}$ (ng/mL)	
	Odds Ratio	P-Value	Odds Ratio	P-Value	Odds Ratio	P-Value
>Grade 1 Diarrhea	1.018 (1.000, 1.037)	0.055	1.001 (1.000, 1.001)	0.033	1.013 (1.001, 1.025)	0.034
>Grade 2 Diarrhea	1.000 (0.990, 1.010)	0.956	1.000 (1.000, 1.000)	0.537	0.997 (0.990, 1.004)	0.368
>Grade 3 Diarrhea	1.003 (0.992, 1.014)	0.632	1.000 (1.000, 1.000)	0.901	0.998 (0.991, 1.006)	0.655
>Grade 3 Fatigue	1.002 (0.975, 1.029)	0.901	1.000 (0.999, 1.001)	0.969	1.000 (0.982, 1.018)	0.993
Rash	0.996 (0.983, 1.009)	0.521	1.000 (0.999, 1.000)	0.475	0.997 (0.988, 1.006)	0.474
Elevated Liver Enzyme Level	0.998 (0.987, 1.008)	0.646	1.000 (1.000, 1.000)	0.770	0.999 (0.992, 1.006)	0.799

Such an increase in neratinib exposure should not be of concern given the flat exposure-response (E-R) relationship on systemic toxicity. Supportive E-R analyses for safety in patients with advance/metastatic breast cancer (n = 345) suggested no apparent relationship between systemic neratinib exposure and the safety endpoints of any grade diarrhoea (≥ grade 1), ≥ grade 2 diarrhoea, ≥ grade 3 diarrhoea, ≥ grade 3 fatigue, elevated liver enzyme levels, and ≥ grade 1 rash (Figure).

Relationship of Safety Endpoints and Area-Under-the-Curve at Steady State of Neratinib in Patients with Advanced Breast Cancers



ExteNET

A10. Priority question: Please provide the full clinical study report (CSR), including all sections, figures, appendices as well as protocol amendments, for this trial.

We are sending four additional sets of documentation regarding the ExteNET trial:

- 3144a2-3004-ww: all sections of ExteNET CSR, dated 20 April, 2016
- 3144a2-3004-ww_wwaddendum: Addendum report for the ExteNET CSR (interim 5-year results) dated 31 May, 2016
- European Medicines Agency (EMA) re-examination briefing book
- EMA re-examination request for information dated 15 May, 2018

A11. Priority question: Please present results for all primary and secondary endpoints in the label population:

a. by node status (0 vs. 1-3 vs. 4 or more and unknown) as stated in your pre-planned analyses). If the definition of the node status differs in some analyses, please explain and clarify. Ideally, patients that are node-negative should be classified as "0".

b. by geographic region as well as separately for the UK patients,

c. by subgroups based on the time passed since completion of trastuzumab treatment, e.g. for patients who are treated ≤ 3 months, between 3 and 6 months, and ≥ 6 months from trastuzumab treatment.

Included below are all primary and secondary efficacy analyses by nodal status, geographic region, and time from completion of trastuzumab treatment.

a) As stated in the investigational plan in the CSR dated 20 April, 2016, randomisation was stratified by nodal status (0, 1-3, 4 or more positive nodes). Patients with residual invasive disease in the breast but node-negative or unknown nodal status in the axilla after neoadjuvant therapy were included under 1-3 positive nodes. Baseline characteristics of the label population (see response to Q16) show only 29 patients (2.2%) in the label population had unknown nodal status, with similar distribution between treatment arms (14 with neratinib and 15 with placebo).

b) For geographic region, the appropriate preplanned subgroup includes Western Europe, Australia, and South Africa. The UK was not a preplanned subgroup and the number of UK patients is too small to perform an appropriate statistical test (N = 41; 19 in the neratinib arm and 22 in the placebo arm).

Figure 14.2.9.4.1. Forest Plot of 2-year Disease-free Survival for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in the ITT Population

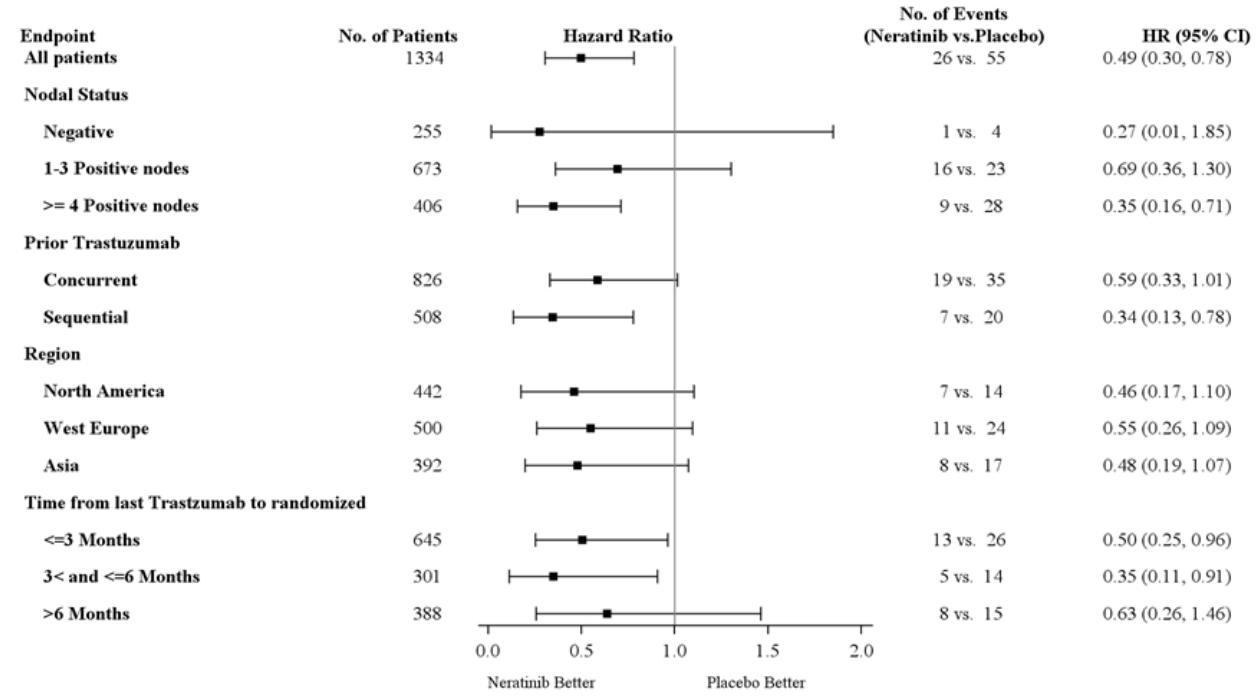


Figure 14.2.9.4.2. Forest Plot of 5-year Disease-free Survival for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in the ITT Population

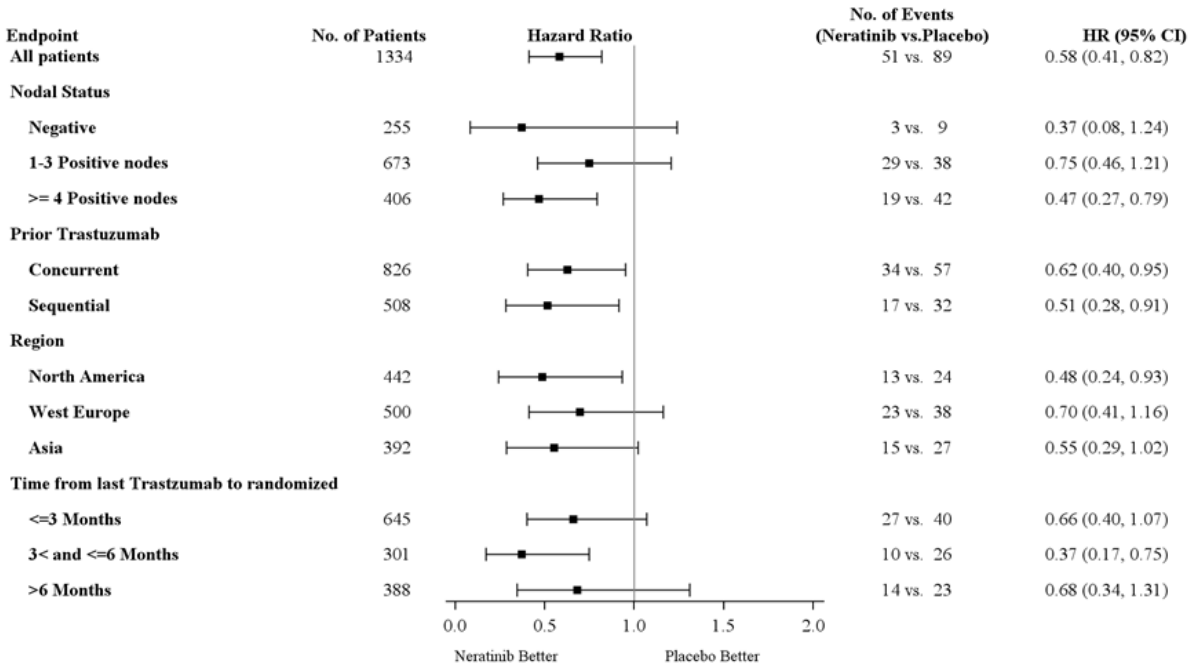


Figure 14.2.9.4.3. Forest Plot of 2-year Disease-free Survival Including DCIS for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in the ITT Population

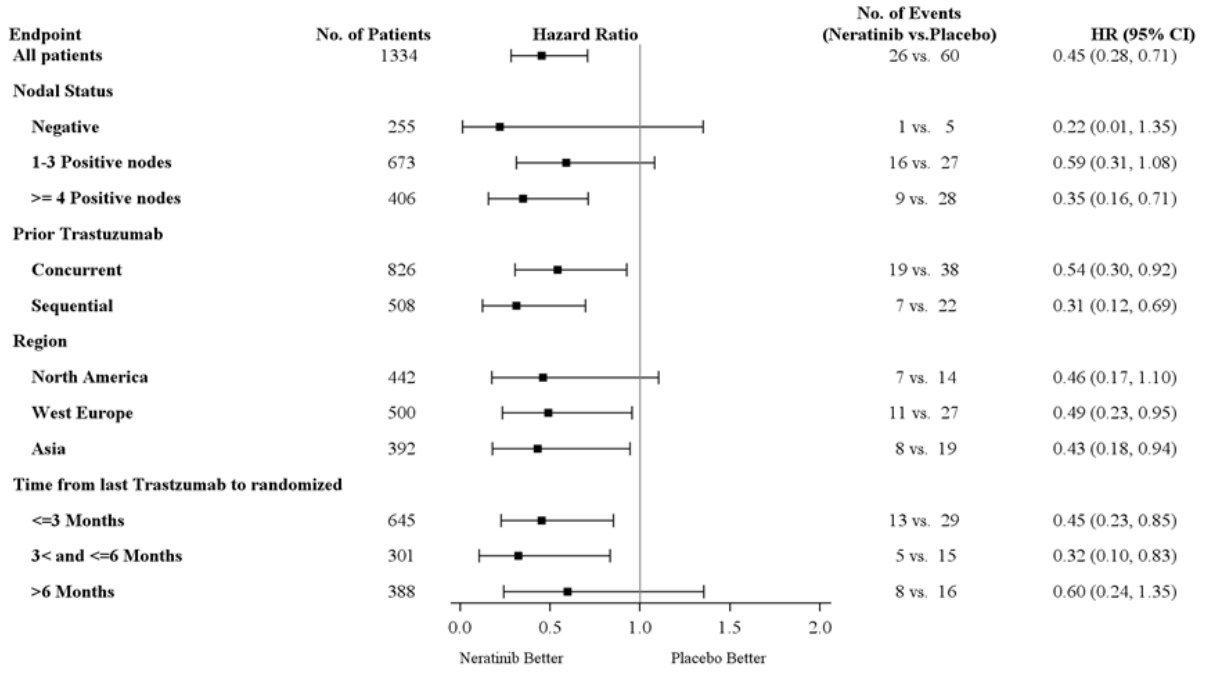


Figure 14.2.9.4.4. Forest Plot of 5-year Disease-free Survival Including DCIS for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in the ITT Population

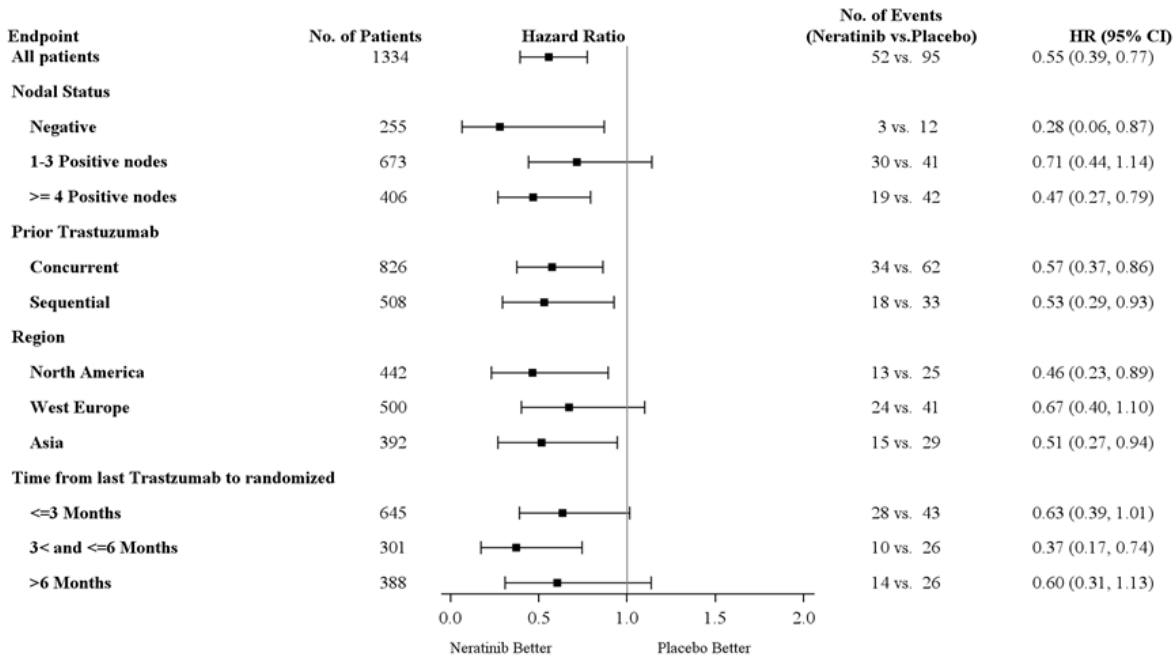


Figure 14.2.9.4.5. Forest Plot of 2-year Distant Disease-free Survival for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in the ITT Population

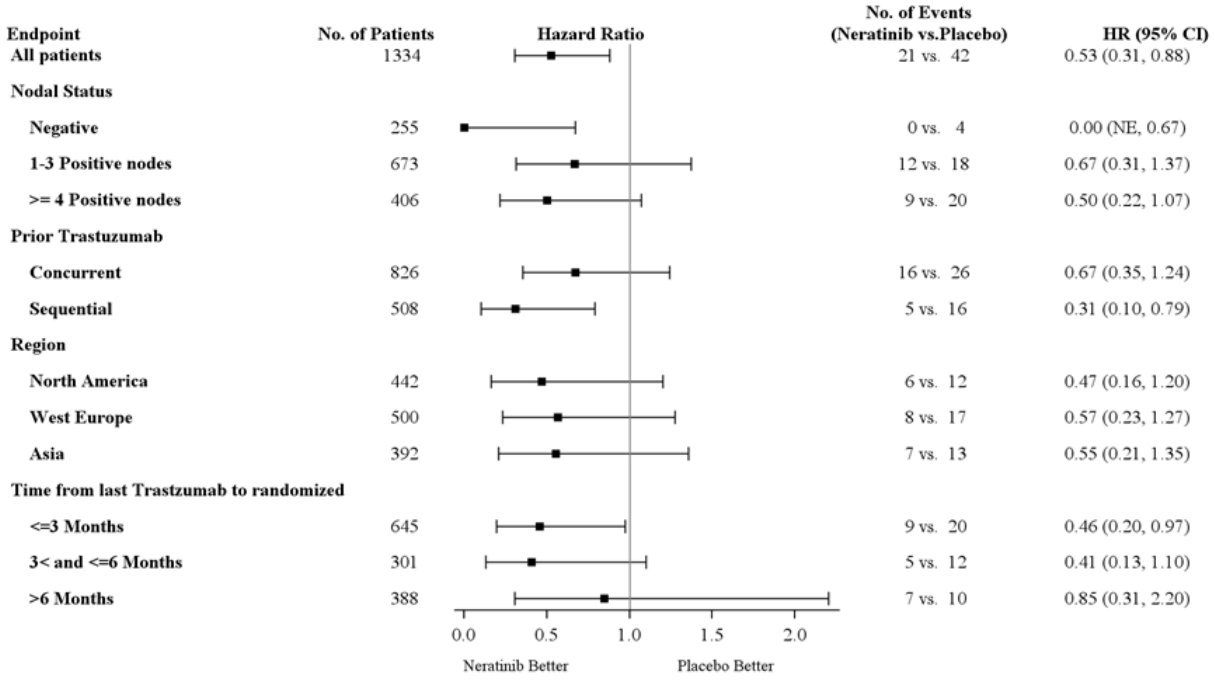


Figure 14.2.9.4.6. Forest Plot of 5-year Distant Disease-free Survival for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in the ITT Population

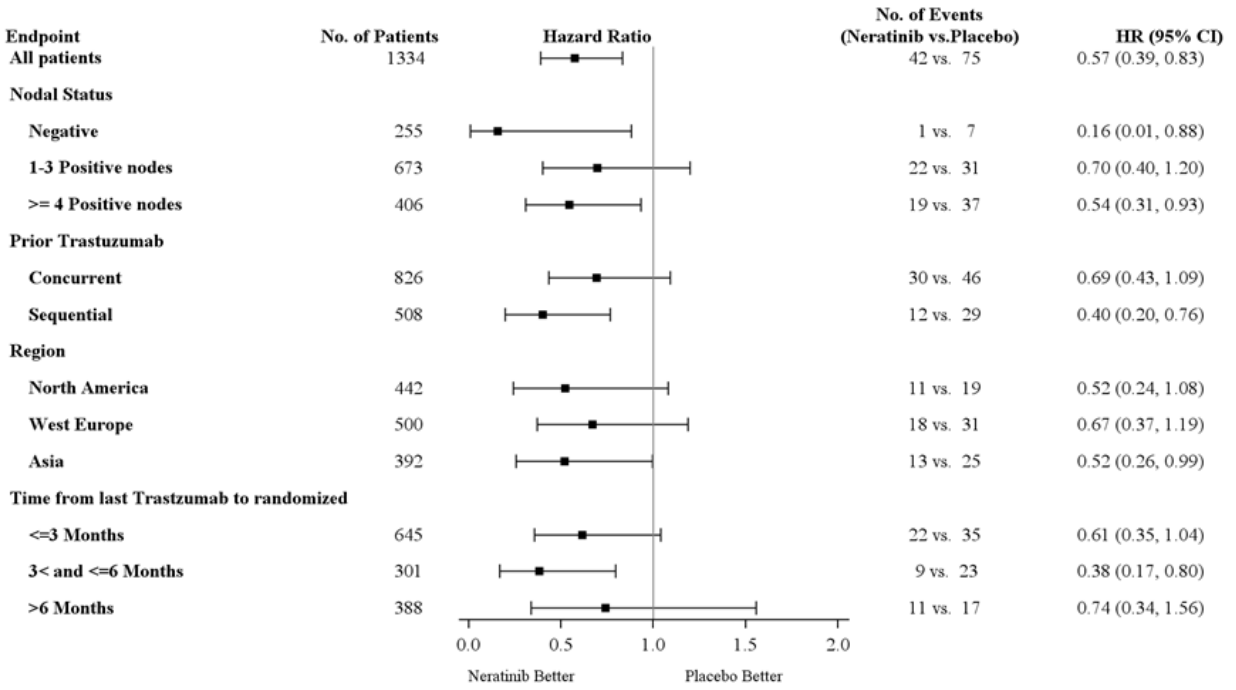


Figure 14.2.9.4.7. Forest Plot of 2-year Time to Distant Recurrence for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in the ITT Population

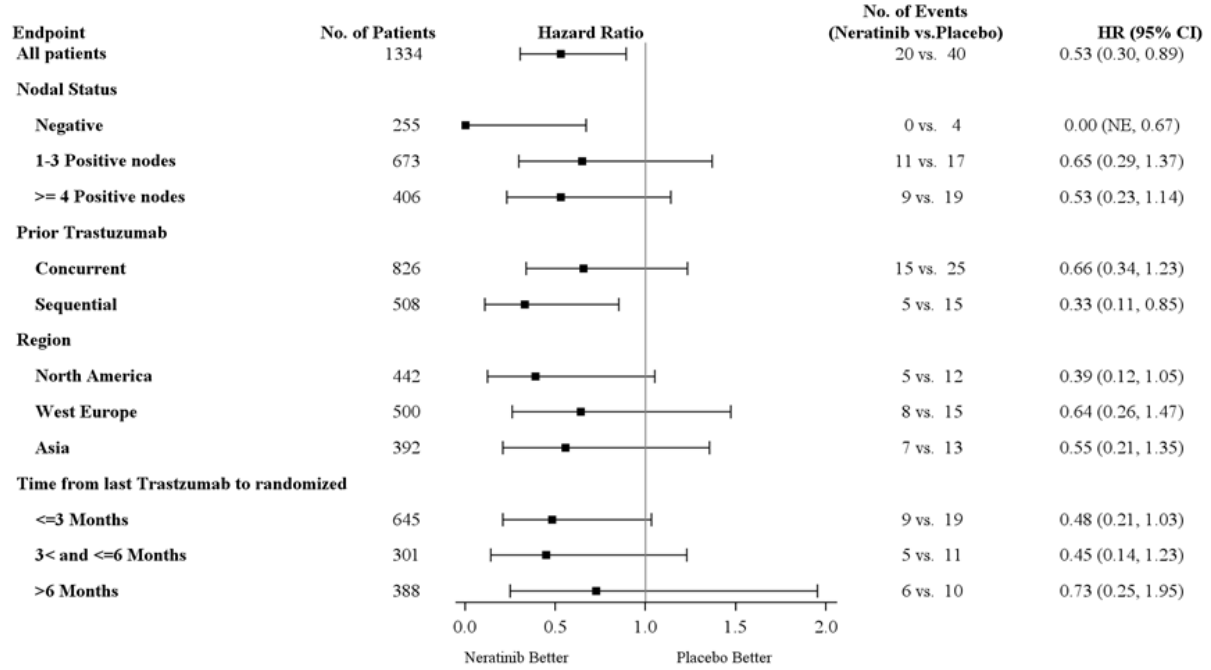
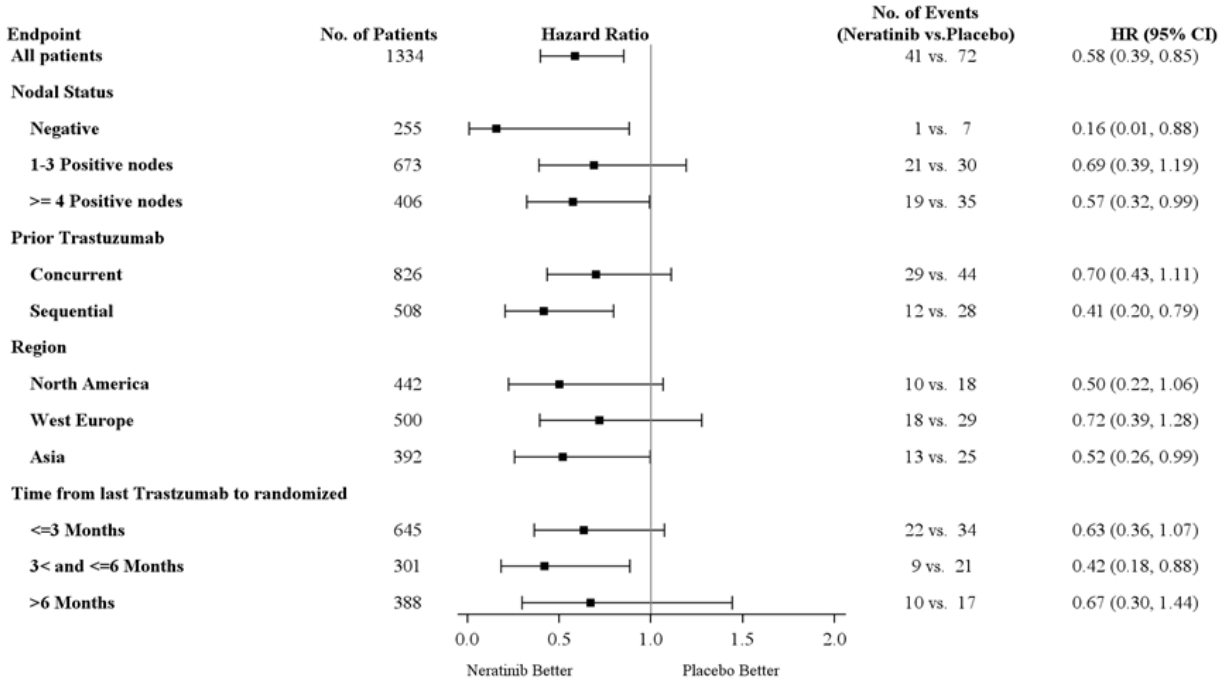


Figure 14.2.9.4.8. Forest Plot of 5-year Time to Distant Recurrence for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in the ITT Population



A12. Priority question: Please provide interim results for the secondary endpoint “overall survival”, either according to the interim analysis outlined in

Table 3 or ideally a more recent analysis of the label population (see also question B13).

The only overall survival (OS) data currently available were presented in the dossier in Section B.2.6.1.3 [redacted] After amendment 13, the interim analysis at 124 events (described in Table 6 of Document B) was no longer planned, and the analysis above was conducted at 5-years follow-up, as stated in Martin et al. (2017).

A13. Priority question: Regarding managing diarrhoea,

a. please report the number of participants who had prophylaxis for diarrhoea,

b. kindly provide results comparing different subgroups (e.g. different types and dosages of prophylaxis) for patients in the label population.

a) In ExteNET, no mandatory antidiarrhoeal prophylaxis was specified in the protocol. However, investigators were instructed to treat diarrhoea reactively at its earliest occurrence, and if significant diarrhoea persisted, loperamide or other antidiarrhoeal medications were recommended. A summary of antidiarrhoeal medication used in the label safety population is shown in Table 14.6.2.4 below.

b) As concomitant antidiarrhoeal prophylaxis was not mandated in ExteNET, there were no prespecified subgroups for patients using different types and doses of antidiarrhoeal medication, so efficacy results are not available. For safety, the incidence of treatment-emergent diarrhoea in those patients in the label population taking antidiarrhoeal medications is shown in Table 14.6.2.4.1.

Table 14.6.2.4. Summary of Antidiarrhoeal Medications for Hormone-Receptor Positive and Prior Adjuvant Trastuzumab ≤ 1 Year Patients, Safety Population

	Neratinib (N = 662)	Placebo (N = 657)	Total (N = 1,319)
Any antidiarrhoeal medication, n (%)	[redacted]	[redacted]	[redacted]
Antidiarrhoeal medication name, n (%)	[redacted]	[redacted]	[redacted]
▪ Loperamide	[redacted]	[redacted]	[redacted]
▪ Antibiotics	[redacted]	[redacted]	[redacted]
▪ Diphenoxylate / Atropine	[redacted]	[redacted]	[redacted]
▪ Probiotics	[redacted]	[redacted]	[redacted]
▪ Acetorphan	[redacted]	[redacted]	[redacted]
▪ Octreotide	[redacted]	[redacted]	[redacted]
▪ Other	[redacted]	[redacted]	[redacted]
Time to first antidiarrhoeal medication (days)	[redacted]	[redacted]	[redacted]
▪ n	[redacted]	[redacted]	[redacted]
▪ Mean	[redacted]	[redacted]	[redacted]
▪ Median (SD)	[redacted]	[redacted]	[redacted]
▪ Q1, Q3	[redacted]	[redacted]	[redacted]
▪ Min, Max	[redacted]	[redacted]	[redacted]
Number of patients receiving prophylactic antidiarrhoeal medication, n (%)	[redacted]	[redacted]	[redacted]

Table 14.6.2.4.1. Summary of Characteristics of Treatment-emergent Diarrhea taking Anti-diarrheal Prophylaxis treatment for Hormone-receptor Positive and Prior Adjuvant Trastuzumab <=1 Year Patients, Safety Population

	Neratinib [redacted]	Placebo [redacted]
Any diarrhoea	[redacted]	[redacted]
Serious	[redacted]	[redacted]
Treatment related	[redacted]	[redacted]
Serious treatment related	[redacted]	[redacted]
Action taken		
▪ IP discontinuation	[redacted]	[redacted]
▪ Withdrawal from study	[redacted]	[redacted]
▪ IP reduction	[redacted]	[redacted]
▪ Temporarily stopping IP	[redacted]	[redacted]
▪ Hospitalisation	[redacted]	[redacted]
▪ Concomitant medication	[redacted]	[redacted]
▪ Other	[redacted]	[redacted]
Maximum toxicity, n (%)		
▪ Grade 1	[redacted]	[redacted]
▪ Grade 2	[redacted]	[redacted]
▪ Grade 3	[redacted]	[redacted]
▪ Grade 4	[redacted]	[redacted]
Outcome of the last diarrhoea episode, n (%)		
▪ Persisted	[redacted]	[redacted]
▪ Resolved	[redacted]	[redacted]

	Neratinib [redacted]	Placebo [redacted]
Time to first onset in days (any grade)		
▪ n	[redacted]	[redacted]
▪ Mean (SD)	[redacted]	[redacted]
▪ Median	[redacted]	[redacted]
▪ Q1, Q3	[redacted]	[redacted]
▪ Min, max	[redacted]	[redacted]
Cumulative duration per patient in days (any grade)		
▪ n	[redacted]	[redacted]
▪ Mean (SD)	[redacted]	[redacted]
▪ Median	[redacted]	[redacted]
▪ Q1, Q3	[redacted]	[redacted]
▪ Min, max	[redacted]	[redacted]
Number of episodes per patient (any grade)		
▪ n	[redacted]	[redacted]
▪ Mean (SD)	[redacted]	[redacted]
▪ Median	[redacted]	[redacted]
▪ Q1, Q3	[redacted]	[redacted]
▪ Min, max	[redacted]	[redacted]

A14. Priority question: Please provide a table with patient numbers showing all concomitant and subsequent endocrine therapy received in the ExteNET trial, in intervention and placebo groups, for the label population.

a) Concomitant endocrine therapy is shown in Table 14.6.2.3.0 below. Subsequent endocrine therapy after end-of-study treatment was not collected in ExteNET.

Table 14.6.2.3.0. Summary of Concomitant Endocrine Therapy for Patients with Hormone-receptor Positive and Prior Adjuvant Trastuzumab <=1 Year in ITT Population

	Neratinib (N=670)	Placebo (N=664)	Total (N=1334)
Hormone receptor positive patients	[redacted]	[redacted]	[redacted]
Concomitant endocrine therapy use			
▪ Yes	[redacted]	[redacted]	[redacted]
▪ No	[redacted]	[redacted]	[redacted]
Concomitant endocrine therapy - n (%)			
▪ Antioestrogen and aromatase inhibitor	[redacted]	[redacted]	[redacted]
▪ Antioestrogen only	[redacted]	[redacted]	[redacted]
▪ Aromatase inhibitor only	[redacted]	[redacted]	[redacted]
▪ Non-antioestrogen and aromatase inhibitor	[redacted]	[redacted]	[redacted]

Hormone receptor status using stratification factor.
The denominator for concomitant endocrine therapy use yes/no is based on patients with corresponding hormone receptor status.
The denominator for the type of endocrine therapy is based on patients who had concomitant endocrine therapy.

A15. Priority question: Regarding patients with residual invasive disease,

a. please justify why patients with residual invasive disease after neoadjuvant therapy were permitted to be entered in the trial, despite an inclusion criterion of "margins clear of invasive carcinoma",

b. kindly provide the number of patients with residual invasive disease in the breast in the ExteNET trial, in intervention and placebo groups, for the label population

c. please clarify what constituents as the primary outcome measure invasive- disease free survival (iDFS) in patients who already had residual invasive disease.

a) Patients who had neoadjuvant therapy (i.e. therapy before surgery) had to have some residual invasive disease in order to proceed to surgery and adjuvant trastuzumab therapy and thus be eligible for the ExteNET trial. As noted in the CSR, residual disease had to be invasive (i.e. not just ductal carcinoma in situ [DCIS]) and limited to the breast. Patients would then have progressed to surgery, and the requirement for "margins clear of invasive carcinoma" had to be met at this stage.

b) Following surgery, no patients had residual invasive disease as this would have precluded inclusion.

c) As no patients had residual invasive disease at the time of study entry, iDFS was the primary outcome in all patients.

A16. Priority question: The CONTROL trial inclusion criteria included stage I-IIIC breast cancer. Whereas, the ExteNET trial included stage II-IIIC breast cancer. Please clarify whether neratinib is expected to be used in patients with stage I breast cancer (excluded from the main trial).

In the original 2009 protocol, all patients stage I-IIIc were included in the main ExteNET trial, and are included in the main ITT and label populations presented in the company submission. Data presented in Table 14.1.6.19 below show that 9.9% of the label population presented in the CS had stage I breast cancer.

Global Amendment 3 in 2010 revised the inclusion criteria for breast cancer staging and nodal status to include only patients with stage II-IIIc and only patients with axillary node-positive disease. The rationale for this amendment was in light of data from two adjuvant trastuzumab trials (NCCTG N9831 and BCIRG 006) that suggested that patients are at higher risk of recurrence closer to completion of adjuvant trastuzumab and that the risk of recurrence may decrease over time. As such, the study design and eligibility criteria were revised to include only patients with a higher risk of recurrence, i.e. node-positive patients only and within 1 year from completion of prior trastuzumab therapy.

As part of this amendment, the “amended ITT” (aITT) population, consisting of all patients randomised under Amendment 3, and all patients randomised prior to implementation of Amendment 3 if they meet two key eligibility criteria: (1) node-positive disease, and (2) randomisation within 1 year of completion of prior trastuzumab, was specified. However, as per the EMA label, neratinib is indicated for all patients with HR+/HER2 early-stage breast cancer, including stage I patients. Therefore, the aITT population is narrower than the EMA label population since it is restricted to patients with stage II-IIIc breast cancer, and was not presented in the CS.

Table 14.1.6.19. Baseline Disease Characteristics for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients and in the ITT Population

	Neratinib (N=670)	Placebo (N=664)	Total (N=1334)
ECOG Performance Status - n (%)			
0	625 (93.3)	605 (91.1)	1230 (92.2)
1	43 (6.4)	57 (8.6)	100 (7.5)
Unknown	2 (0.3)	2 (0.3)	4 (0.3)
Nodal Status[a] - n (%)			
Negative	130 (19.4)	125 (18.8)	255 (19.1)
1-3 Positive Nodes	339 (50.6)	334 (50.3)	673 (50.4)
>= 4 Positive Nodes	201 (30.0)	205 (30.9)	406 (30.4)
Prior Trastuzumab[a] - n (%)			
Concurrent	411 (61.3)	415 (62.5)	826 (61.9)
Sequential	259 (38.7)	249 (37.5)	508 (38.1)
Menopausal Status at Diagnosis - n (%)			
Premenopausal	350 (52.2)	342 (51.5)	692 (51.9)
Postmenopausal	320 (47.8)	322 (48.5)	642 (48.1)
Stage - n (%)			
I	69 (10.3)	63 (9.5)	132 (9.9)
IIA	153 (22.8)	136 (20.5)	289 (21.7)
IIB	129 (19.3)	129 (19.4)	258 (19.3)
IIIA	124 (18.5)	125 (18.8)	249 (18.7)
IIIB	16 (2.4)	13 (2.0)	29 (2.2)
IIIC	64 (9.6)	65 (9.8)	129 (9.7)
Unknown	115 (17.2)	133 (20.0)	248 (18.6)

[a] From stratification factors

Table 14.1.6.19. Baseline Disease Characteristics for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients and in the ITT Population

	Neratinib (N=670)	Placebo (N=664)	Total (N=1334)
T-stage - n (%)			
T1	218 (32.5)	209 (31.5)	427 (32.0)
T2	270 (40.3)	250 (37.7)	520 (39.0)
T3 And Above	61 (9.1)	65 (9.8)	126 (9.4)
Unknown	121 (18.1)	140 (21.1)	261 (19.6)
N-stage - n (%)			
0	160 (23.9)	158 (23.8)	318 (23.8)
1	304 (45.4)	290 (43.7)	594 (44.5)
2	128 (19.1)	136 (20.5)	264 (19.8)
3	64 (9.6)	65 (9.8)	129 (9.7)
Unknown	14 (2.1)	15 (2.3)	29 (2.2)
Histology Grade - n (%)			
Undifferentiated	5 (0.7)	8 (1.2)	13 (1.0)
Poorly Differentiated	266 (39.7)	292 (44.0)	558 (41.8)
Moderately Differentiated	254 (37.9)	228 (34.3)	482 (36.1)
Well Differentiated	42 (6.3)	29 (4.4)	71 (5.3)
Unknown	103 (15.4)	107 (16.1)	210 (15.7)
Primary Cell Type - n (%)			
Ductal Carcinoma	625 (93.3)	616 (92.8)	1241 (93.0)
Lobular Carcinoma	32 (4.8)	28 (4.2)	60 (4.5)
Tubular/Cribriform	3 (0.4)	9 (1.4)	12 (0.9)
Mucinous	3 (0.4)	6 (0.9)	9 (0.7)
Medullary	1 (0.1)	2 (0.3)	3 (0.2)
Metaplastic	0	0	0
Adenoid Cystic	0	0	0
Missing	6 (0.9)	3 (0.5)	9 (0.7)

Table 14.1.6.19. Baseline Disease Characteristics for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients and in the ITT Population

	Neratinib (N=670)	Placebo (N=664)	Total (N=1334)
Time from Diagnosis to Randomization (month)			
n	669	664	1333
Mean (SD)	21.23 (5.56)	21.17 (5.06)	21.20 (5.31)
Median	20.30	20.67	20.47
Q1, Q3	17.45, 24.41	17.38, 24.33	17.45, 24.41
Min, Max	7.7, 60.2	7.8, 43.5	7.7, 60.2

A17. Please provide the number of participants in the label population who had neratinib dose reductions as well as the timings of dose reductions and the corresponding number of tablets for each dose.

A full dose of neratinib is 240 mg, administered as six 40 mg tablets per day.

Table 14.3.0.2.14. Summary of Dose Reduction for Hormone-receptor Positive and Prior Adjuvant Trastuzumab <=1 Year Patients, Safety Population

	Neratinib (N=662)	Placebo (N=657)
Patients With Dose Reduction [a] - n (%)		
No Dose Reduction	425 (64.2)	608 (92.5)
One Or More Dose Reduction	237 (35.8)	49 (7.5)
Lowest Dose Reduction Level - n (%)		
No Dose Reduction	425 (64.2)	608 (92.5)
Reduce To 200 mg/day	116 (17.5)	27 (4.1)
Reduce To 160 mg/day	72 (10.9)	6 (0.9)
Reduce To <160 mg/day	49 (7.4)	16 (2.4)
Reduce To 180 mg/day [b]	0 (0.0)	0 (0.0)
Dose Reduction Reason - n (%)		
Reduced Due To AE	203 (30.7)	13 (2.0)
Non-compliance	43 (6.5)	35 (5.3)
Other [c]	110 (16.6)	6 (0.9)
Time to first dose reduction (days)		
N	237	49
Mean (SD)	58.84 (75.67)	122.94 (106.45)
Median	28.00	100.00
Q1, Q3	14.00, 73.00	28.00, 188.00
Min, Max	1.0, 374.0	1.0, 371.0

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The chinese patients are defined as patients from mainland China, Taiwan, and Hong Kong
[a]Patient is considered to have dose reduction if the total daily dose taken (actual dose) is < 240 mg/day and > 0 mg/day.
[b]One patient's dose was reduced to 180 mg/day and then subsequently increased to 240 mg/day.
[c]Other includes any other reasons given for dose reduction.
Dose reduction reasons are not mutually exclusive.

A18. In Table 7 and Table 8 in document B of the CS, participants in the neratinib and placebo groups are identified as having prior neoadjuvant or adjuvant therapy that is identified as being neither anthracycline or taxane. Please identify what this therapy was.

The number of ExteNET patients in the label population who received neoadjuvant or adjuvant therapy that was neither a taxane or an anthracycline and details of therapy type are shown in Tables 14.1.7.21 and 14.1.7.26. According to the CSR,

this could also be a cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) regimen. Prior therapy with an HER1 and/or HER2 inhibitor other than trastuzumab (such as pertuzumab) was an exclusion criterion in the ExteNET trial, so none of these patients should have received pertuzumab according to the protocol (only 1 patient in the placebo arm reported prior neoadjuvant therapy with pertuzumab).

Table 14.1.7.21. Prior Anti-cancer Therapy for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in IIT Population

	Neratinib (N=670)	Placebo (N=664)	Total (N=1334)
Prior Radiotherapy - n (%)			
No	139 (20.7)	112 (16.9)	251 (18.8)
Yes	531 (79.3)	552 (83.1)	1083 (81.2)
Prior Surgery - n (%)			
Lumpectomy only	225 (33.6)	237 (35.7)	462 (34.6)
Mastectomy	445 (66.4)	427 (64.3)	872 (65.4)
Prior Anti-cancer Medication - n (%)			
Yes	670 (100.0)	664 (100.0)	1334 (100.0)
Anti-cancer Medication Type - n (%)			
Trastuzumab	670 (100.0)	664 (100.0)	1334 (100.0)
Anthracycline only	67 (10.0)	58 (8.7)	125 (9.4)
Anthracycline + Taxane	435 (64.9)	445 (67.0)	880 (66.0)
Taxane only	167 (24.9)	159 (23.9)	326 (24.4)
Neither Anthracycline or Taxane	1 (0.1)	2 (0.3)	3 (0.2)
Prior Neo-adjuvant Therapy - n (%)			
No	508 (75.8)	472 (71.1)	980 (73.5)
Yes	162 (24.2)	192 (28.9)	354 (26.5)
Neo-adjuvant Therapy Type			
Trastuzumab	107 (16.0)	131 (19.7)	238 (17.8)
Anthracycline only	19 (2.8)	18 (2.7)	37 (2.8)
Anthracycline + Taxane	96 (14.3)	128 (19.3)	224 (16.8)
Taxane only	45 (6.7)	44 (6.6)	89 (6.7)
Neither Anthracycline or Taxane	2 (0.3)	2 (0.3)	4 (0.3)
Pathological Complete Response Status			
Pathologic Complete Response	17 (2.5)	21 (3.2)	38 (2.8)
No Pathologic Complete Response	131 (19.6)	164 (24.7)	295 (22.1)
Unknown	14 (2.1)	7 (1.1)	21 (1.6)

[a]From stratification factors.
One month is defined as 365.25/12 days, and one year is defined as 365.25 days.

Table 14.1.7.21. Prior Anti-cancer Therapy for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in IIT Population

	Neratinib (N=670)	Placebo (N=664)	Total (N=1334)
Prior Adjuvant Therapy - n (%)			
No	2 (0.3)	0	2 (0.1)
Yes	668 (99.7)	664 (100.0)	1332 (99.9)
Adjuvant Therapy Type			
Trastuzumab	667 (99.6)	662 (99.7)	1329 (99.6)
Anthracycline only	71 (10.6)	63 (9.5)	134 (10.0)
Anthracycline + Taxane	330 (49.3)	299 (45.0)	629 (47.2)
Taxane only	139 (20.7)	145 (21.8)	284 (21.3)
Neither Anthracycline or Taxane	128 (19.1)	157 (23.6)	285 (21.4)
Time from Last Trastuzumab to Randomization (month)			
n	670	664	1334
Mean (SD)	4.25 (3.34)	4.37 (3.50)	4.31 (3.42)
Median	3.07	3.30	3.19
Q1, Q3	1.54, 6.51	1.35, 6.93	1.38, 6.77
Min, Max	0.2, 12.0	0.3, 12.0	0.2, 12.0
Duration of Prior Adjuvant Trastuzumab (month)			
n	667	662	1329
Mean (SD)	10.89 (2.50)	10.86 (2.56)	10.88 (2.53)
Median	11.40	11.43	11.43
Q1, Q3	10.84, 11.96	10.74, 11.93	10.78, 11.93
Min, Max	1.4, 29.1	1.4, 24.0	1.4, 29.1
Time from Last Trastuzumab to Randomization			
<= 1 Year	670 (100.0)	664 (100.0)	1334 (100.0)
Prior Endocrine Therapy Use for Hormone Positive[a] Patients - n (%)			
No	38 (5.7)	30 (4.5)	68 (5.1)
Yes	632 (94.3)	634 (95.5)	1266 (94.9)

[a]From stratification factors.
One month is defined as 365.25/12 days, and one year is defined as 365.25 days.

Table 14.1.7.21. Prior Anti-cancer Therapy for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in IIT Population

	Neratinib (N=670)	Placebo (N=664)	Total (N=1334)
Anti-estrogen only	340 (50.7)	317 (47.7)	657 (49.3)
Anti-estrogen & aromatase inhibitor	29 (4.3)	24 (3.6)	53 (4.0)
Aromatase inhibitor only	259 (38.7)	290 (43.7)	549 (41.2)
Non anti-estrogen & aromatase inhibitor	4 (0.6)	3 (0.5)	7 (0.5)

Table 14.1.7.26. Prior Anti-cancer Therapy for Hormone Receptor-positive and Prior Adjuvant Trastuzumab <=1 Year Patients in IIT Population

	Neratinib (N=670)	Placebo (N=664)
Prior Neo-adjuvant Therapy - n (%)		
Neither Anthracycline or Taxane	2 (0.3)	2 (0.3)
Goserelin	1 (0.1)	0 (0.0)
Pertuzumab	0 (0.0)	1 (0.2)
Tamoxifen	1 (0.1)	1 (0.2)
Trastuzumab	0 (0.0)	1 (0.2)
Prior Adjuvant Therapy - n (%)		
Neither Anthracycline or Taxane	128 (19.1)	157 (23.6)
Anastrozole	24 (3.6)	30 (4.5)
Capecitabine	3 (0.4)	3 (0.5)
Cyclophosphamide	2 (0.3)	1 (0.2)
Cyclophosphamide W/Fluorouracil/Methotrex	0 (0.0)	1 (0.2)
Exemestane	5 (0.7)	11 (1.7)
Fluorouracil	2 (0.3)	1 (0.2)
Gemcitabine	0 (0.0)	1 (0.2)
Goserelin	4 (0.6)	10 (1.5)
Goserelin Acetate	3 (0.4)	2 (0.3)
Letrozole	18 (2.7)	32 (4.8)
Leuprorelin	1 (0.1)	1 (0.2)
Leuprorelin Acetate	10 (1.5)	9 (1.4)
Methotrexate	1 (0.1)	2 (0.3)
Methotrexate Sodium	1 (0.1)	0 (0.0)
Tamoxifen	56 (8.4)	58 (8.7)
Tamoxifen Citrate	24 (3.6)	23 (3.5)
Trastuzumab	127 (19.0)	155 (23.3)
Triptorelin	2 (0.3)	3 (0.5)
Vinorelbine Tartrate	0 (0.0)	2 (0.3)

Page 1 of 1

A19. Please provide subgroup analyses for the label population for nodal status and concurrent/sequential trastuzumab regimen, for other outcomes listed (disease-free survival including ductal carcinoma in situ (DFS-DCIS), distant disease-free survival (DFS) and time to distant recurrence (TTDR)).

See response to A11.

CONTROL

A20. Priority question: Please provide the full CSR, including all sections, figures, appendices as well as protocol amendments, for this trial.

We are sending one additional set of documentation regarding the CONTROL trial:

- Puma-ner-6201: all sections of the interim CONTROL safety report, dated 24 February, 2016

A21. Please discuss the applicability of CONTROL to a UK population, given none of the testing centres are based in the UK.

The original cohorts of CONTROL did not include European sites, but cohorts currently in recruitment include sites in Spain. However, the loperamide prophylaxis regimens used in the study are aligned with antidiarrhoeal medications commonly used in UK clinical practice to treat chemotherapy-induced diarrhoea, so results of CONTROL are applicable to the UK (confirmed by clinical input provided in Appendix M in the company submission).

A22. Please clarify why oral budesonide and colestipol were added for cycle 1? Why and how were these medications chosen for this trial?

As shown in Figure 3 of Document B, amendments 3 and 4 introduced two new cohorts to the CONTROL study, the budesonide or colestipol cohorts, which are designed to evaluate the use of agents specifically directed against possible mechanisms of the neratinib-induced diarrhoea, namely the local gastrointestinal inflammation (microcolitis) and bile acid secretion. The additional cohorts will investigate the use of an anti-inflammatory agent (budesonide 9 mg daily added for cycle 1) or a bile acid sequestrant (colestipol 2 g twice daily for cycle 1) given in addition to intensive loperamide prophylaxis in further lowering the incidence of diarrhoea. It is anticipated that the different mechanisms of action of these agents may further reduce the incidence of neratinib-induced diarrhoea when used with loperamide in this patient population. Further cohorts will test additional hypotheses and interventions.

Budesonide will be investigated in the first pilot cohort as a proof-of-principle for the anti-inflammatory effect as it has a high glucocorticosteroid activity. The bile acid sequestrant colestipol is a lipid-lowering agent for oral use, that binds bile acids in the intestine forming a complex that is excreted in the faeces. This nonsystemic action results in a partial removal of bile acids from enterohepatic circulation, preventing their reabsorption. The formation of this complex may counteract neratinib-induced diarrhoea by slowing gastrointestinal transit time and by attenuating the possible irritant effect of bile acids on inflamed gastrointestinal lumen.

Data from the budesonide and colestipol cohorts of CONTROL are not included in the economic model, only the loperamide-only arm.

A23. Please clarify how many patients in the CONTROL trial were of the label population.

In the interim analysis population of CONTROL presented in the CS, 231/321 (72%) of the total ITT population also met the label population criteria (HR+ and <1 year from completion of trastuzumab). By cohort, 101/137 (73.7%) of the loperamide cohort, 45/64 (70.3%) of the budesonide cohort, and 85/120 (70.8%) of the colestipol cohort were also the label population. In the economic model, incidence of diarrhoea from the ITT population of the loperamide only cohort was used.

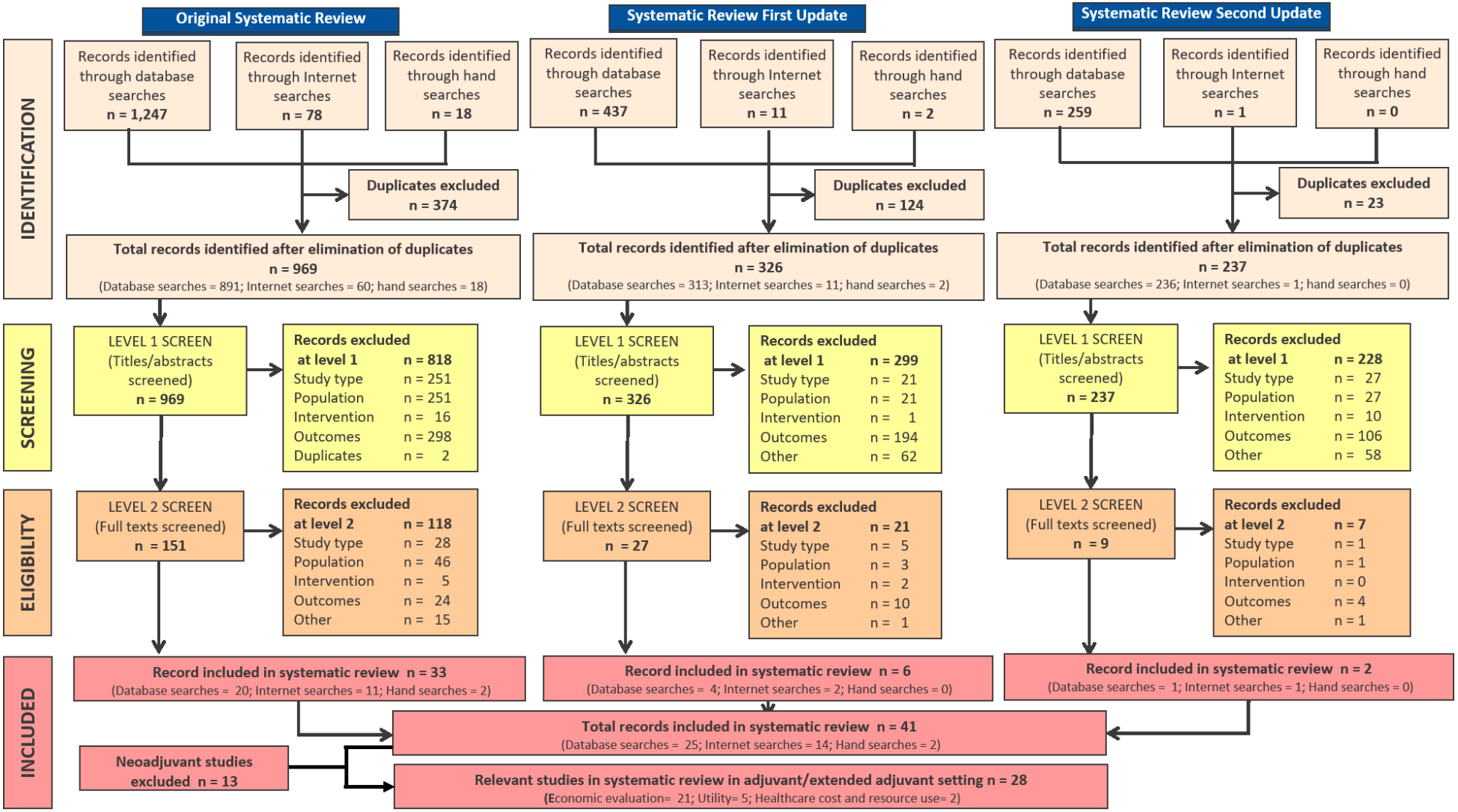
Section B: Clarification on cost-effectiveness data

Literature Search

B1. Please provide the missing PRISMA flow diagram for the economic systematic review (Appendix G; Figure 3, p. 131).

In our version of the CS sent to NICE on 5 February, 2019 the PRISMA diagram is included on page 131. We assume this must be an issue with compatibility between Microsoft Word versions, so we have included it again here for completeness.

PRISMA Flow Diagram for Economic Systematic Review



Clinical inputs

B2. Priority question: Please provide all details of the communication between the company and the clinical experts. Please include anonymised information about the clinical experts, detailed minutes of the face-to-face meeting and/or teleconference, list of expert recommendations and justifications for clinical assumptions and inputs used in the model. In particular, please indicate the following:

a. How many experts provided information for each of the following: model structure, identification of subsequent treatments and their estimated shares in clinical practice, health state resource use and costs, modelling of overall survival (OS), modelling of iDFS and duration of treatment effect?

The table below presents an overview of the clinical input received from UK experts as a response to this question. However, as presented in the submission, further advice was also given by health economic experts.

Input from UK Clinical Experts

	Advice Received					
Advisor - Role (Date)	**Model Structure**	**Identification of Subsequent Treatments and Estimated Shares in Clinical Practice**	**Health State Resource Use and Costs**	**Modelling of Overall Survival**	**Modelling of iDFS**	**Duration of Treatment Effect**
Professor of Oncology at a large UK teaching hospital, principal investigator on several clinical trials (April 2017)	✓			✓	✓	
Clinical senior lecturer and honorary consultant in clinical oncology at a large UK teaching hospital, principal and chief principal investigator on many clinical trials (April 2017)	✓			✓	✓	
Consultant medical oncologist at a London hospital, chief investigator on many national and international trials (December 2018)	✓	✓	✓	✓	✓	✓

b. Please provide further details of the opinions given by experts in relation to each of aspects of the model listed in part a of this question and

provide details regarding the extent to which these opinions were included in the model or justification of why they were not included.

Input from the clinical and health economic experts was received on different occasions and at different stages throughout the development of the economic analysis as the data availability, anticipated population, and overall model evolved. However, these inputs were not elicited through formal interview protocols and, thus, not documented in a formal way that would allow for details of the opinion per expert to be reported as requested in this question. However, opinions given by the experts were reflected throughout the development of the model included in the submission. For example, the input from the external experts drove the selection of data applied when using external data to validate the extrapolation of iDFS, choice of model structure, and incorporation of treatment effect following the trial period.

B3. Priority question: In the submission, many inputs are taken directly from the appraisal of pertuzumab (ID1192). It is not clear how similar the populations are between these different appraisals.

a. Please provide a rationale for assuming similarity between the populations, specifically whether patients would receive same subsequent treatments in practice.

As presented in Appendix M, Puma sought input from a UK clinical expert on the expected subsequent treatment for neratinib patients, who subsequently have a local or distant recurrence. The expert clinical input received confirmed that the expected treatments for treating local and distant recurrence following neratinib were expected to be similar to the treatments and proportions of treatments used in ID1192. Further information around subsequent treatment is also given in the response to question B.23.

b. Kindly justify for each input and each assumption that is taken from ID1192, that they are appropriate for this submission.

Given the similar clinical pathway for patient populations in ID1192 and ExteNET, health state resource use data are aligned with ID1192, as were subsequent treatments received in the local and distant recurrence health states. Other inputs

and assumptions, such as the model structure and patient flow, were validated using ID1192 but were not taken from the submission.

Resource use and costs were aligned with ID1192 with adjustments made to the iDFS health state where the first-year values from ID1192 are removed as patients receiving neratinib will be 1 year further in their treatment and will have finished their course of trastuzumab. Monitoring costs specifically related to neratinib were included, based on clinical input received. The other health states costs reflect recurrence, remission, local recurrence, and distant recurrence, which would be generalisable between the populations in ID1192 and the patients in the ExteNET trial. Subsequent treatment is covered in Question B23.

Model structure and implementation

B4. Priority question: Please provide all input parameters of the model based on the label population, include them in the model and re-run the base-case analysis based on this set of input parameters.

Where possible, all data in the model are reflective of the label population and, thus, no further updates have been incorporated into the model related to this question.

B5. Please summarise the differences and similarities between the economic model used for the current submission and the model used for the pertuzumab appraisal (ID1192).

The submission model was specifically developed for the current appraisal and treatments included. However, given the similar clinical pathway for the patient populations in ID1192 and ExteNET, the model used in the company submission for ID1192 as well as the input provided by the Evidence review group (ERG) and committee were considered to inform the current model development. This was to ensure consistency across the appraisals and to address concerns raised by the ERG and committee for ID1192. Similarities and differences have already been described in Document B. However, some key differences are summarised below.

In ID1192, patients in iDFS were split across two health states; iDFS on-treatment and iDFS off-treatment. The neratinib submission model has one state for iDFS as

all patients will have concluded prior treatment (with the exception of endocrine therapy) and therefore this subdivision is not required.

The metastatic setting is split into first- and second-line treatment in the pertuzumab model in ID1192 and transition probabilities were derived from studies of subsequent lines of therapy. This approach was criticised, and the ERG for ID1192 argued it would have been better to utilize the evidence collected in the clinical trials for pertuzumab in adjuvant therapy of early HER2-postive breast cancer. Based on this criticism, the current model does not specifically model individual lines of therapy in the metastatic setting, but uses the postprogression survival from ExteNET. Further, the pertuzumab model in ID1192 represented postprogression survival using an exponential distribution, to simplify the model structure with regards to time-dependent probabilities. The current model does not have this limitation and allows for time-dependent probabilities (and thus distributions other than the exponential) to be included for postprogression survival.

The survival extrapolations for DFS used in the pertuzumab model in ID1192 did not provide a good fit when compared with that of the HERA trial. Thus, the model incorporated a cure fraction to allow for patients to transition on to general population mortality. However, there were concerns raised about this concept during the assessment. The extrapolation of iDFS in the current model did not have a similar issue with regards to iDFS predictions and, in fact, the model allows for the incorporation of the HERA data to inform the survival extrapolation as a scenario. Therefore, a cure fraction was not incorporated in the current model as the current extrapolations of the trial data are believed to represent long-term iDFS adequately without needing any correction factors.

B6. The primary endpoint for the trial was iDFS, which was defined as the time from randomisation to the first occurrence of one of the following events: 1) Invasive ipsilateral breast tumour recurrence, 2) Local/regional invasive recurrence, 3) Distant recurrence, 4) Death from any cause, 5) Invasive contralateral breast cancer.

Please clarify whether (and how) invasive ipsilateral breast tumour recurrence and invasive contralateral breast cancer were included in the health states of the model.

Invasive ipsilateral breast tumour recurrence and invasive contralateral breast cancer were included as part of local recurrence in the model.

B7. On page 86 in document B of the CS it is mentioned that the "analysis to consider whether a strong correlation between the treatment effect on DFS and the effect of treatment on OS could be identified" were performed. Please provide full details of this analysis.

As presented in Document B, analysis was performed to consider whether a strong correlation between the treatment effect on disease-free survival (DFS) and the treatment effect on OS could be identified. The analysis was performed (as reported in Document B) by analysing the correlation between treatment effect on DFS and treatment effect on OS (trial-level association). This analysis was performed to inform whether variation in treatment effect on OS is explained by variation in treatment effect on DFS. The trials included to investigate the correlation were six randomised controlled trials investigating trastuzumab containing regimens for early breast cancer identified in a recent Cochrane review (Moja et al., 2012). The included trials were those reporting both DFS and OS; B31, BCIRG006, FinHer, HERA, NOAH, and PACS-04 (cited by Moja et al., 2012). The correlation was examined with a weighted linear regression of lnHR DFS on lnHR OS, (weighted by trial size) and resulted in a multiple R-squared of 0.2 and a strong relationship could therefore not be identified.

Treatment effect beyond trial follow-up

B8. Priority question: Table 29 in document B of the CS indicates that "Treatment effect maintained until hazard in iDFS state equal to general population hazard implemented in the base case" is assumed. However, in the model "Assumed continued treatment effect after trial follow-up" is selected. Please clarify the base-case assumption about the duration of the treatment effect.

In the base case, treatment effect is continued without further adjustments after end of trial, while the probability of iDFS is modelled by the extrapolated trial data. However, from the time point the probability of an iDFS event for both treatment arms is based on general population mortality, a treatment effect is implicitly no longer applied, as from this time point both treatments are assumed to be represented by the same hazard of iDFS event, general population mortality.

B9. Priority question: Page 91 in document B of the CS states "the test for non-proportional hazards (Therneau-Grambsch test) also was not significant (Chi-squared = 0.314, P = 0.575)".

a. Please clarify the null hypothesis in this test and whether proportional hazards (between the two arms) for iDFS was assumed.

We can confirm that the null hypothesis of the test is that proportional hazards holds for iDFS between the two treatment arms.

b. Please provide further details on this test, such as the syntax used to conduct the test, the complete outcome (from the used software), the number of observations used to calculate the test statistic, the power of the test, etc

The test was performed in R using the following command: cox.zph. The code used was as follows:

```
# Test whether data is significantly different to the proportional hazard assumption
> zf <- predict(f, type='terms')
> f.short <- cph(S ~ zf, x=T, y=T)
> phtest <- cox.zph(f.short, transform='km')
Output from the above was as follows:
> phtest
          rho chisq     p
Treatment -0.0473 0.314 0.575
```

Further information on the code and test is available at: https://cran.r-project.org/web/packages/survival/survival.pdf

The test was based on the following number of patients: n = 1,334, and the following number of events n = 140. We are not aware of a formula-based power calculation specifically related to the Therneau Grambsch test, however, additional assessments

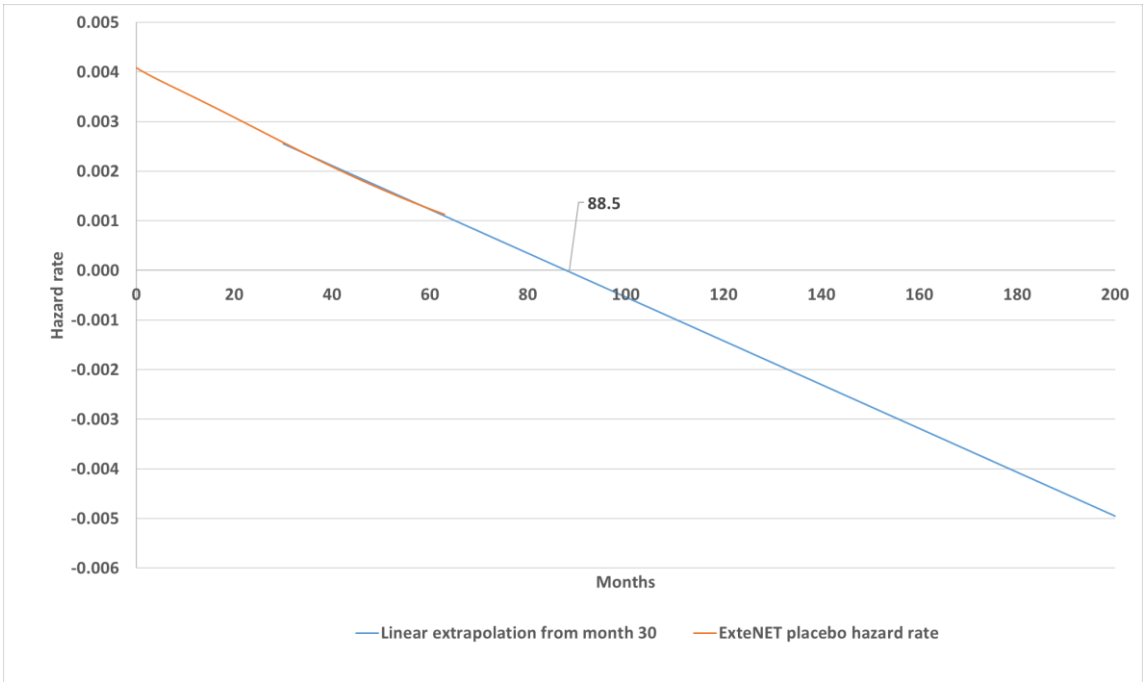
of proportional hazards performed (as described in Document B), did not indicate deviation from the proportional hazards assumption.

B10. Priority question: Figure 32 in document B of the CS shows smoothed hazard rates for DFS from the ExteNET data

a. Please provide extrapolations for the hazard rates in Figure 32 and indicate the time point at which the two curves approximately converge.

During the clarification call the ERG specified that the analysis requested here was a linear extrapolation aligned with what was performed for Figure 33 in Document B. However, extrapolating the hazard rate with a linear regression would lead to non-sensical results. As can be seen from the figure below, extrapolation of the hazard rates for the control arm would lead to a negative hazard at around 88 months from trial onset.

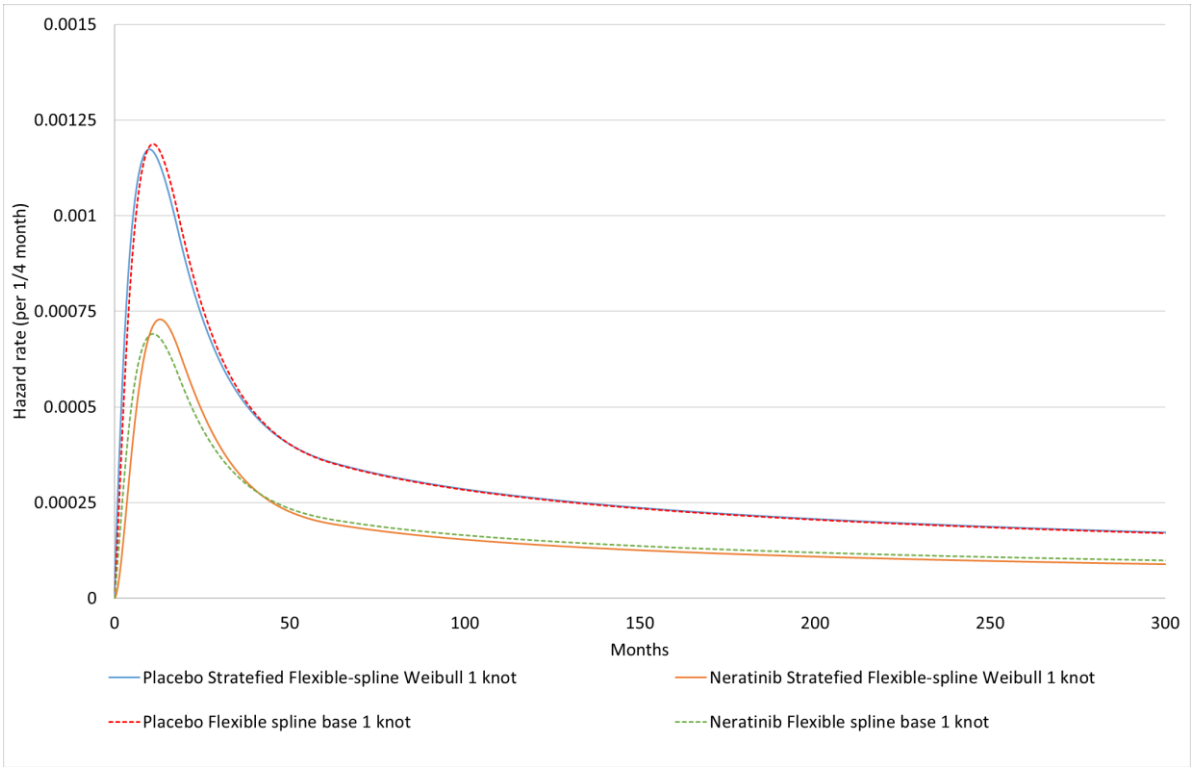
Linear Extrapolation of Placebo Hazard Rates From Month 30



Extrapolations of hazard over time as a response to this question have therefore been included based on the survival analysis performed for iDFS as part of the submission. These analyses have been conducted in line with the Decision Support Unit (DSU) guideline as well as recent methods proposed in the literature. As shown in the submission these extrapolations were well-aligned with the long-term HERA data. The figure below shows the hazard rates for the two arms based on the base-

case distribution used in the model. As can be seen, there is no evidence of the curves for the two arms converging before the hazard rate for both treatment arms would be modelled using general population mortality. As this lack of convergence would be expected due to proportional hazard being assumed in the analyses, we have also included extrapolation of hazard rates based on a stratified analysis (allowing for non-proportional hazards). However, as shown in the figure that scenario also doesn't indicate that the hazard rates will converge.

Extrapolation of Hazard Rates Beyond Trial Follow-Up



b. If Figure 32 was not based on the label population, please provide a similar figure, also indicating the time point at which the two curves approximately converge, for the label population.

Figure 32 was based on the label population.

c. In Appendix L it is also mentioned that different approaches to smoothing the hazard rates may produce different conclusions. Please explore different approaches to smoothing the hazard rates for the label population and compare their conclusions (the time point at which the two curves approximately converge).

As smoothing of the hazard rates was not used in the survival analysis, alternative scenarios for the economic model based on different approaches to smoothing of the hazard rates cannot be presented.

Disease free survival

B11. Please provide the different parametric models fitted to the ExteNET trial data in Figure 14 in Appendix L, separately.

Please find individual plots of each distribution in Figures L14A to L14K included below. For completeness we have also included individual figures for each distribution included in Figure 15 in Appendix L (Figures L15A – L15E).

Figure L14A

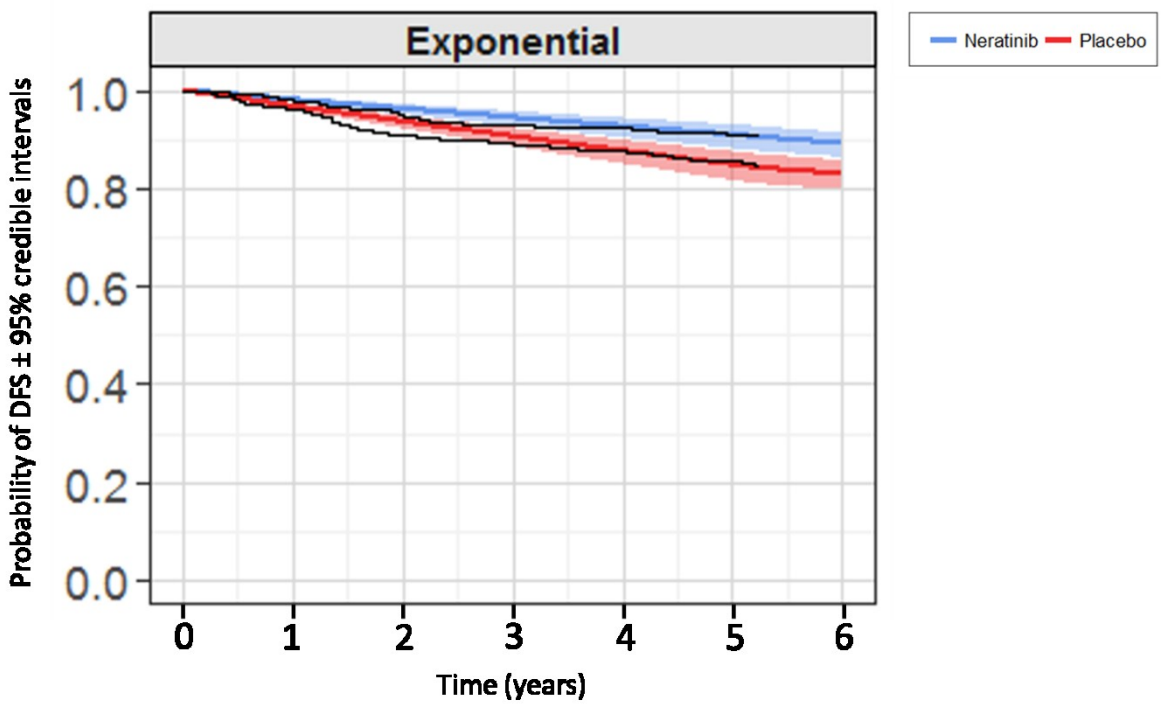


Figure L14B

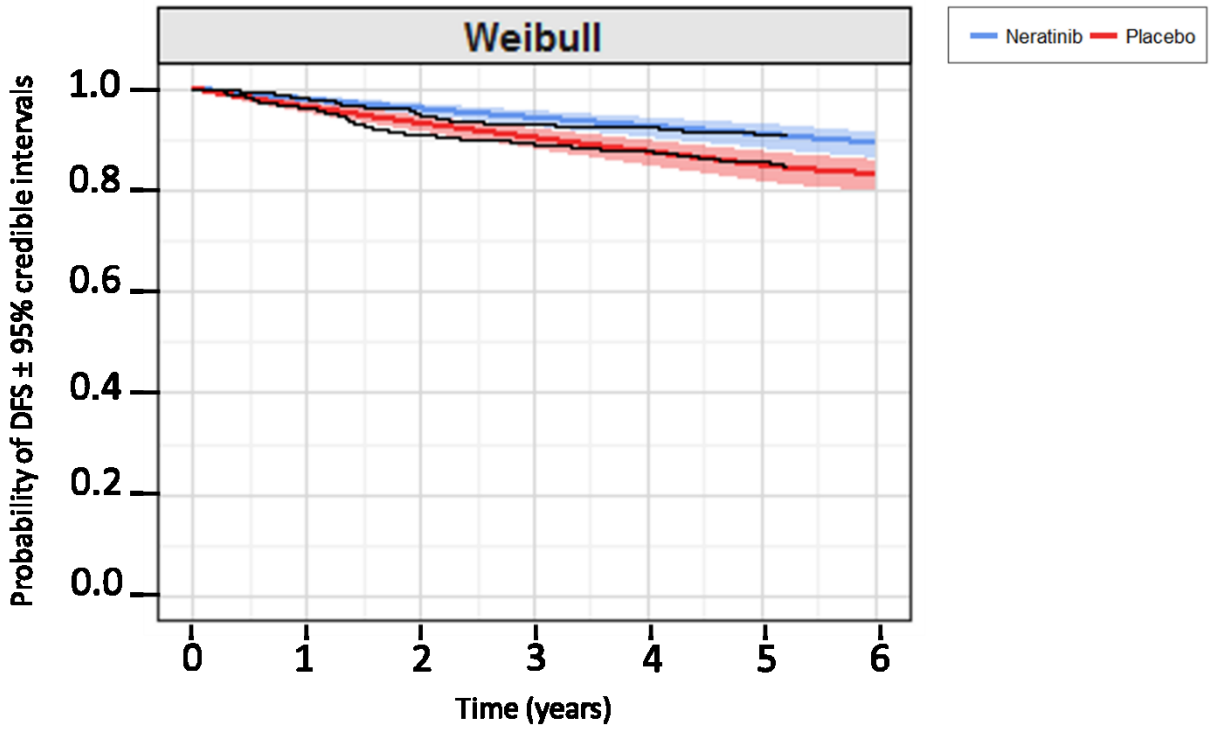


Figure L14C

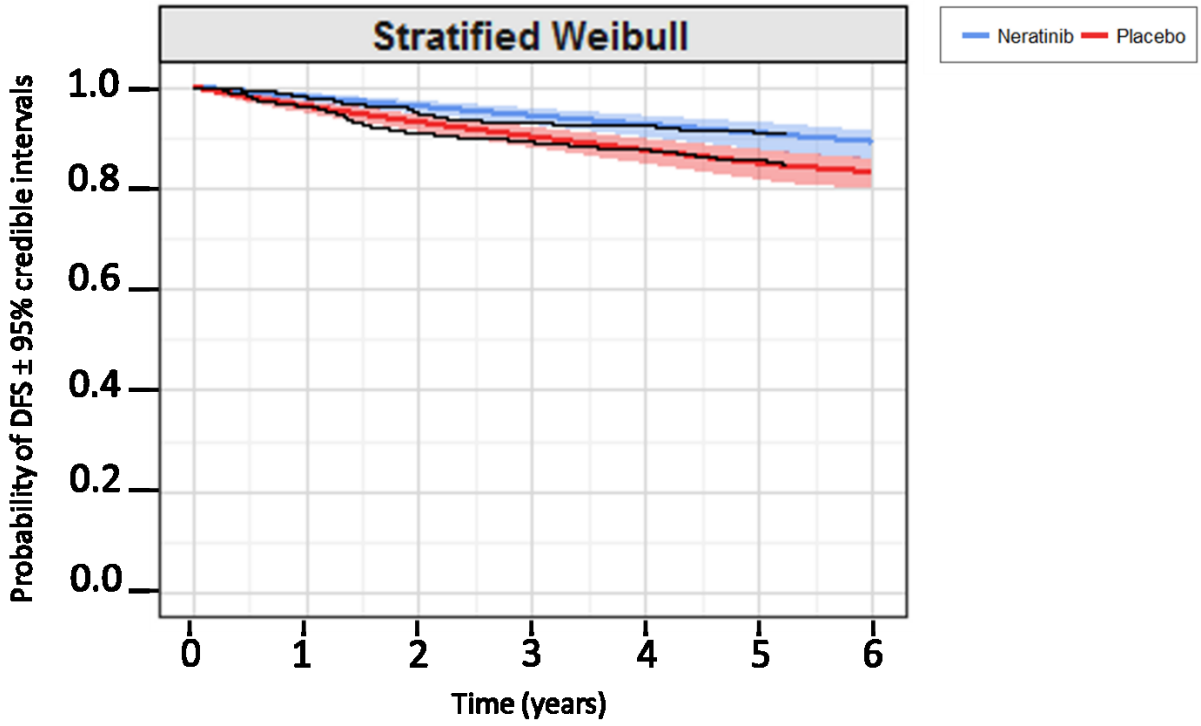


Figure L14D

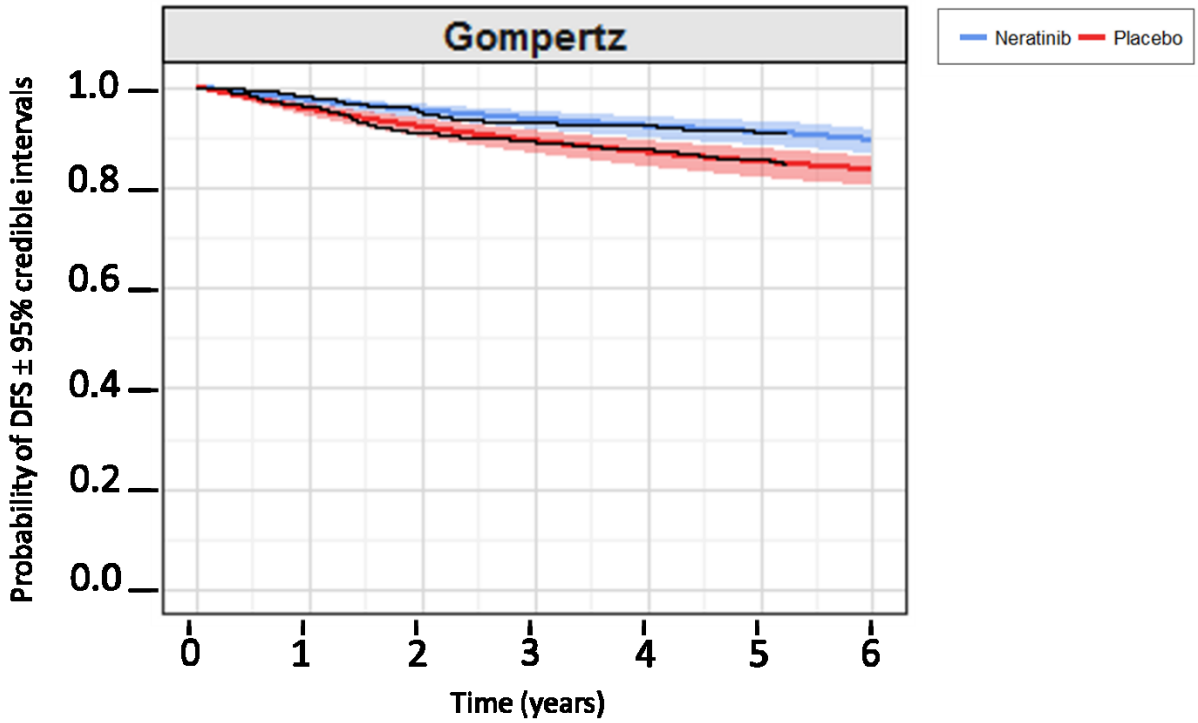


Figure L14E

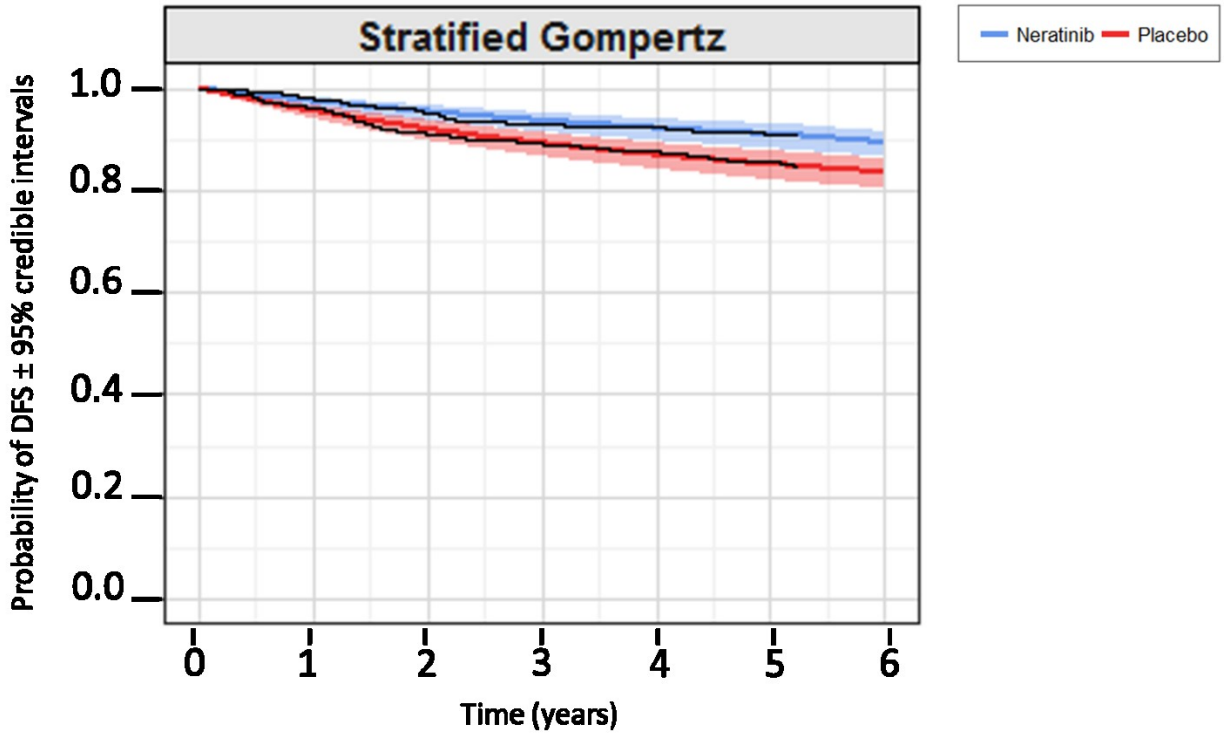


Figure L14F

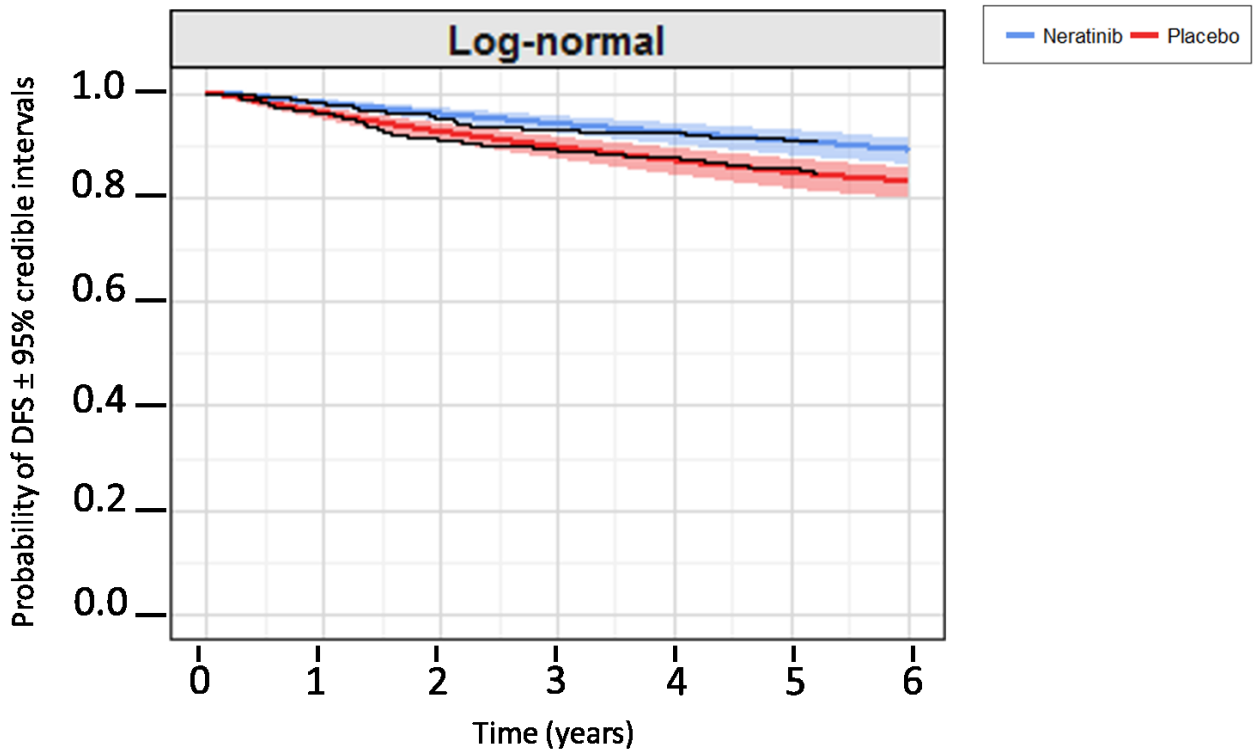


Figure L14G

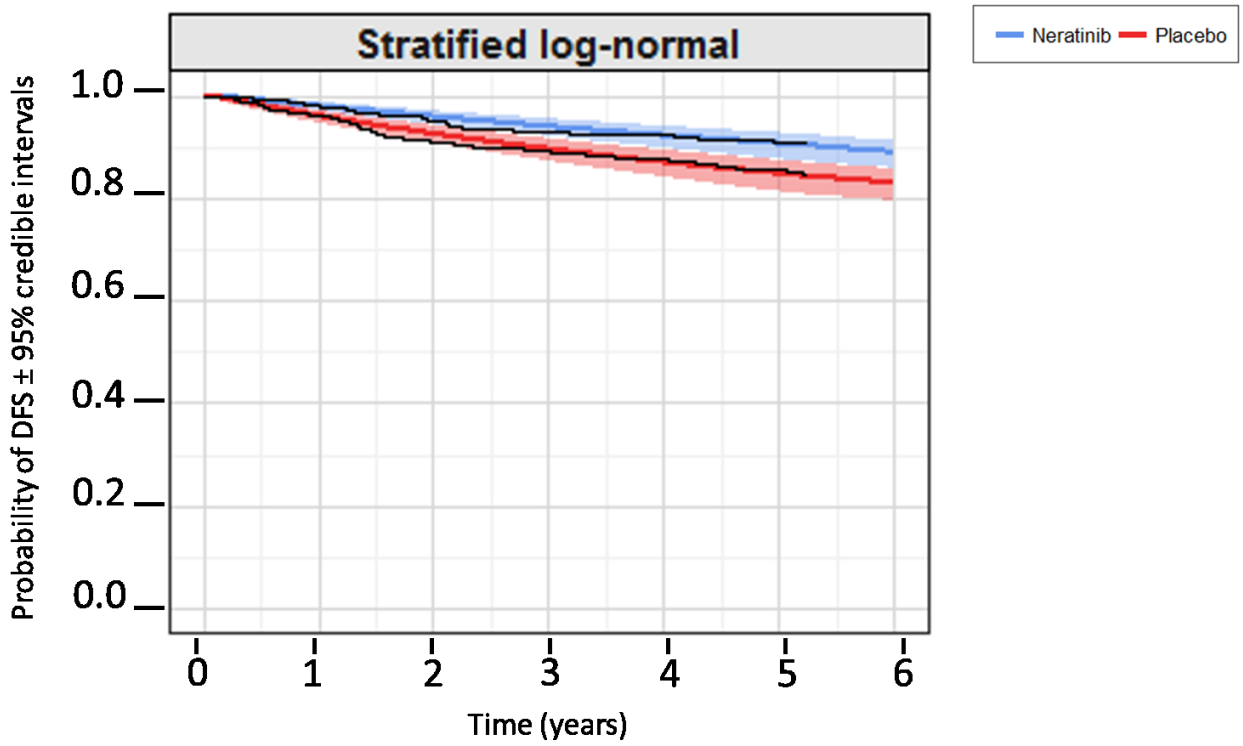


Figure L14H

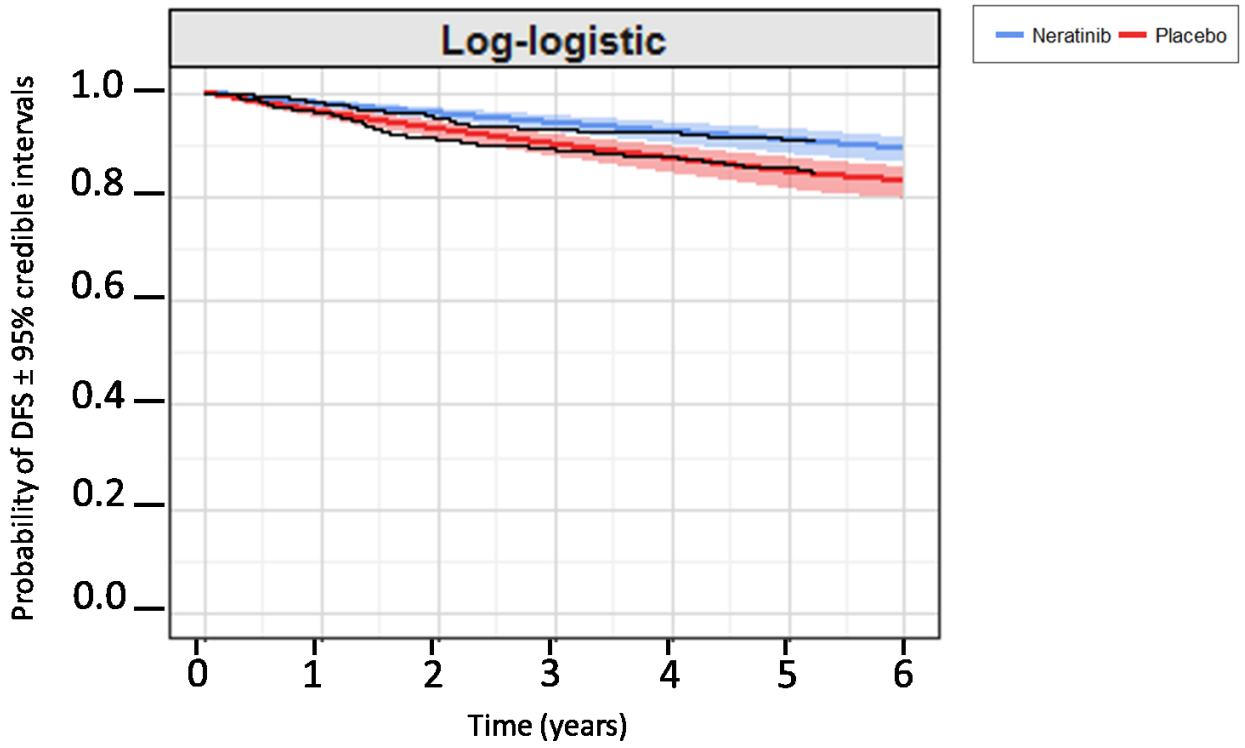


Figure L14I

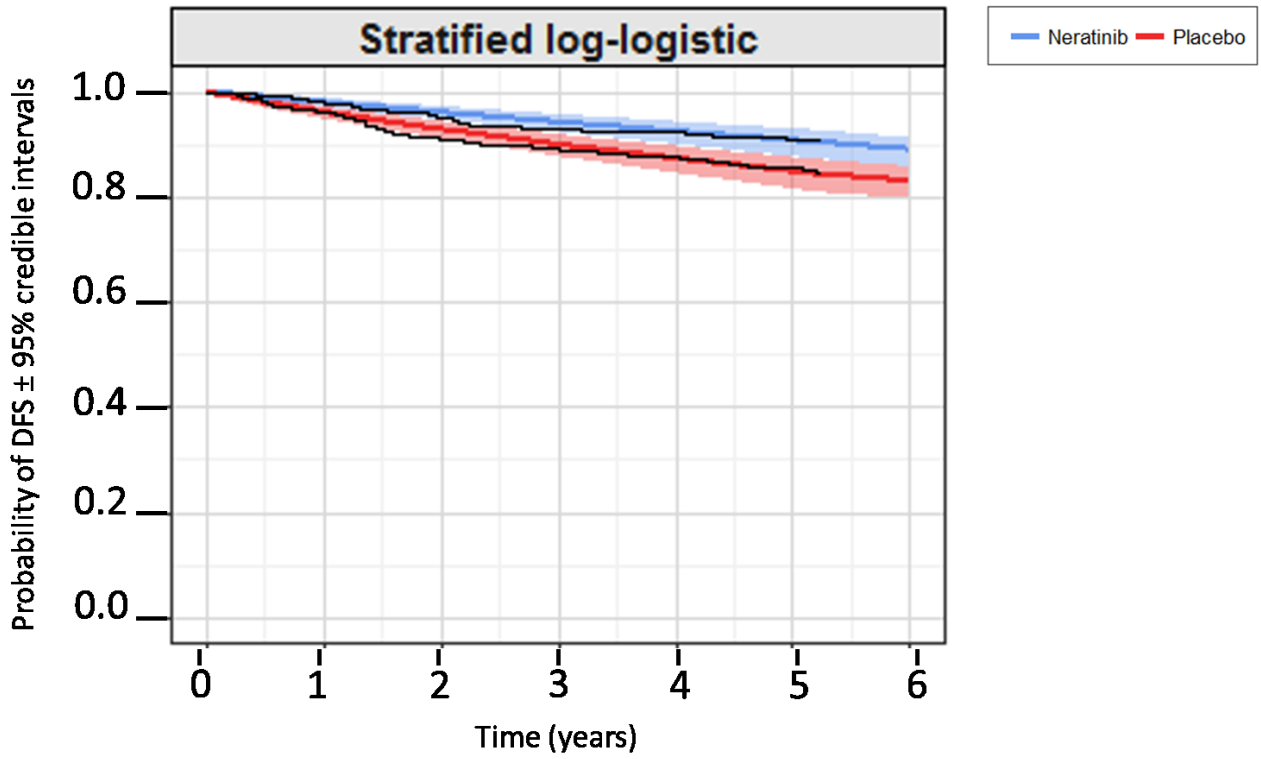


Figure L14J

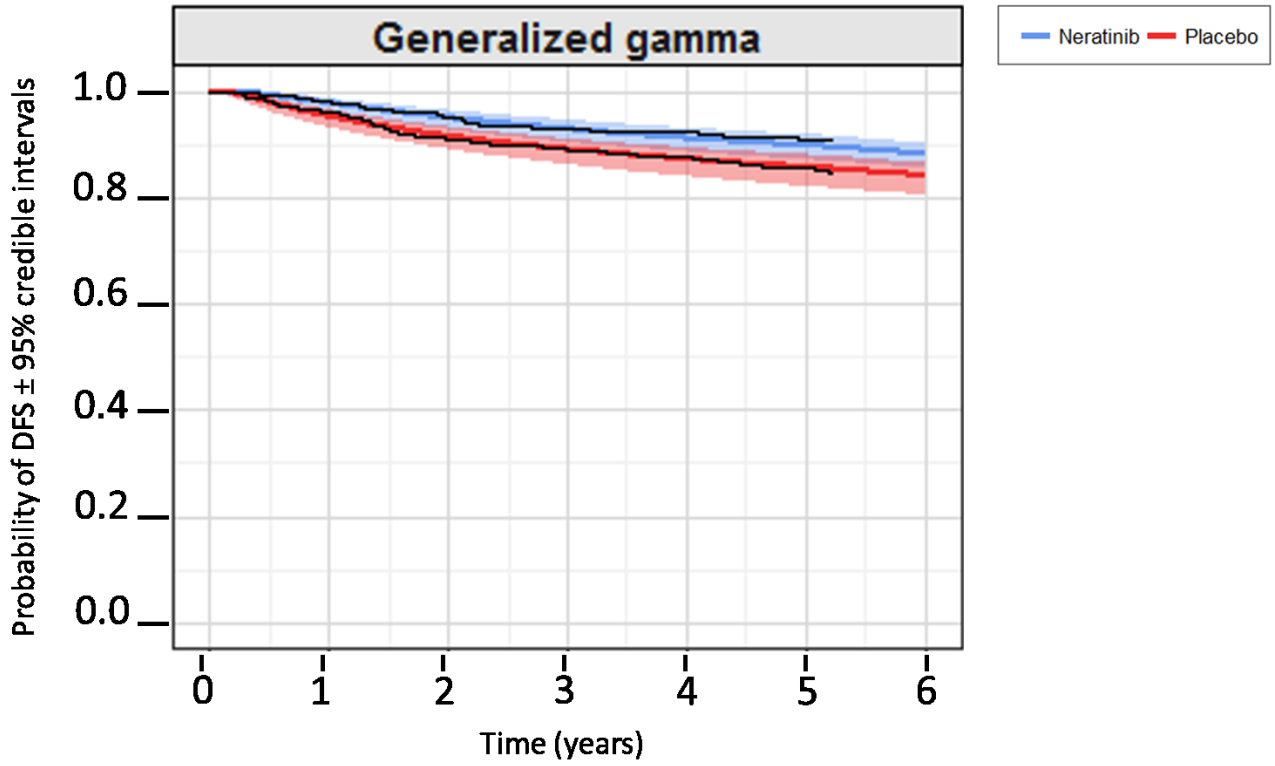


Figure L14K

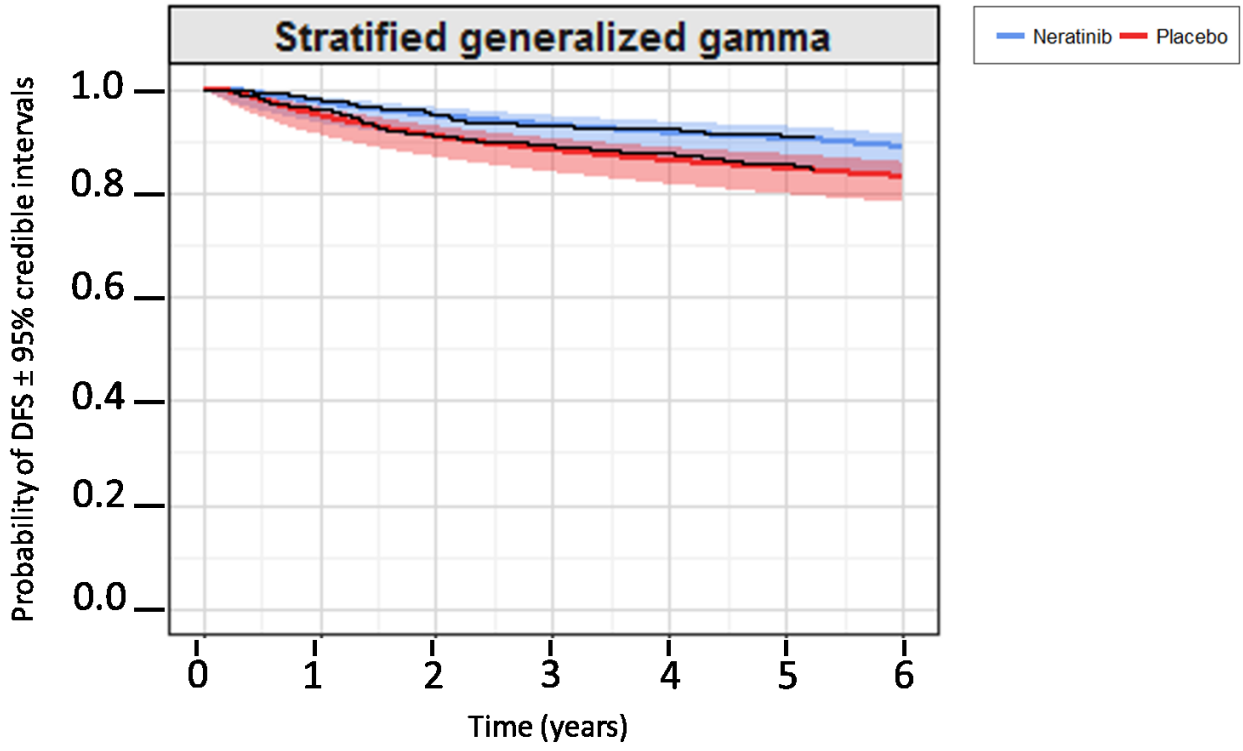


Figure L15A

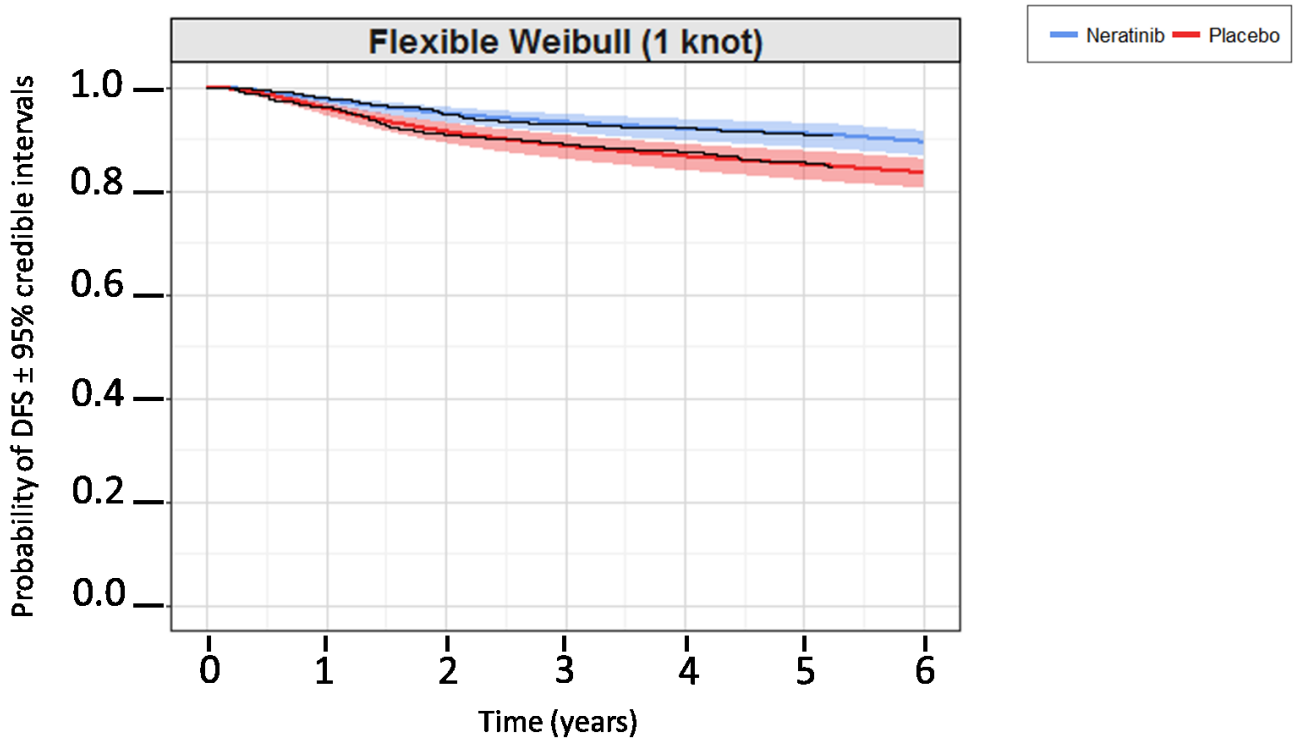


Figure L15B

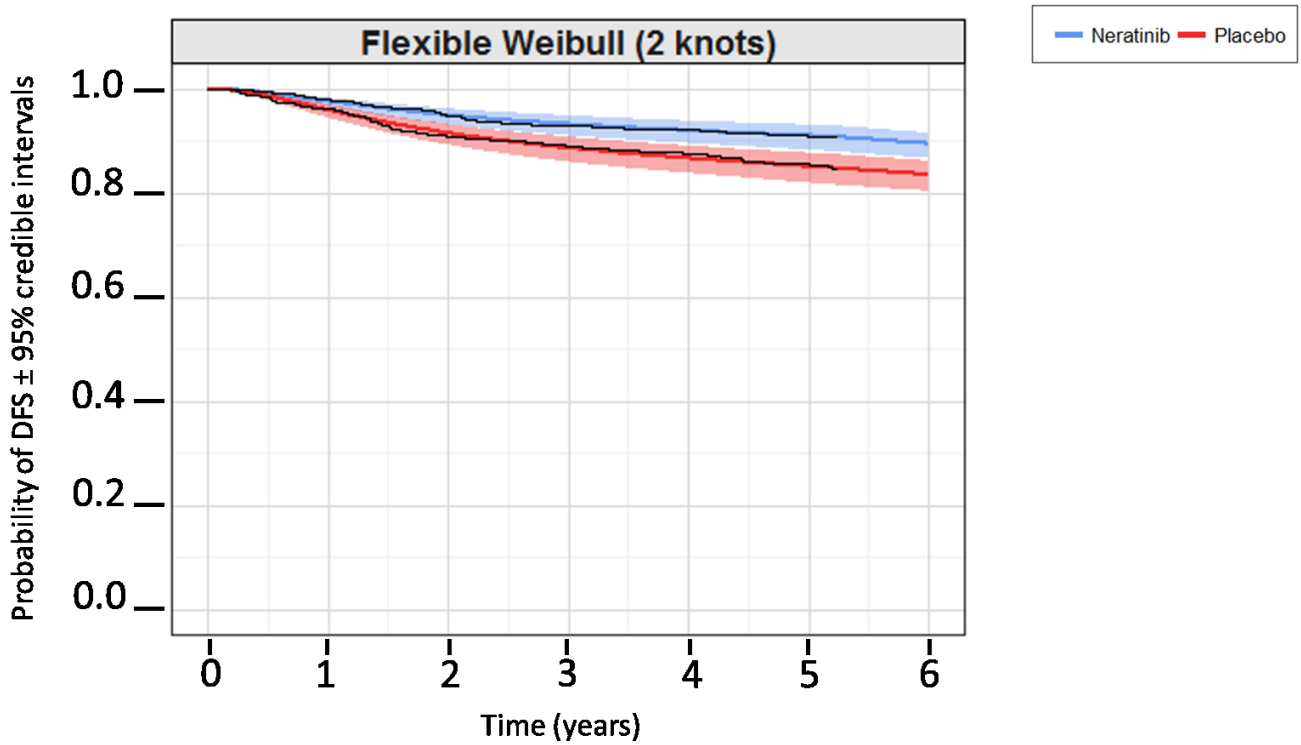


Figure L15C

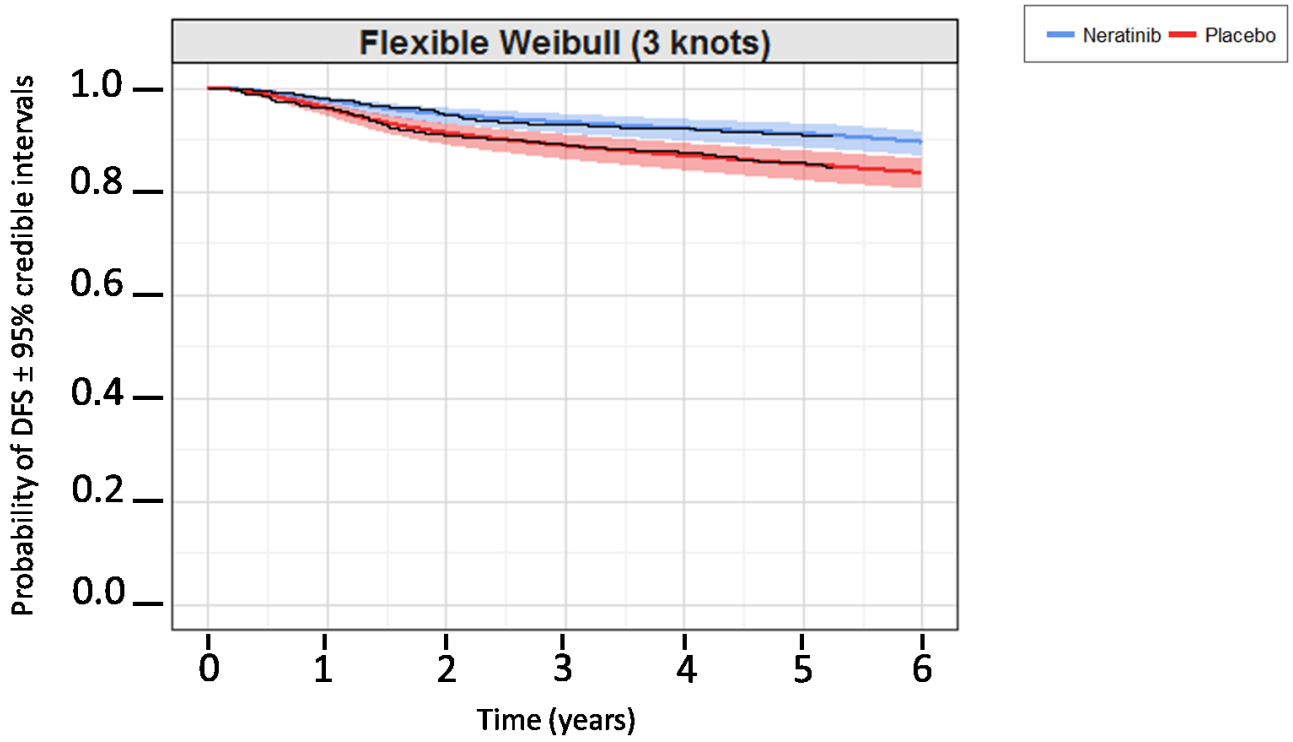


Figure L15D

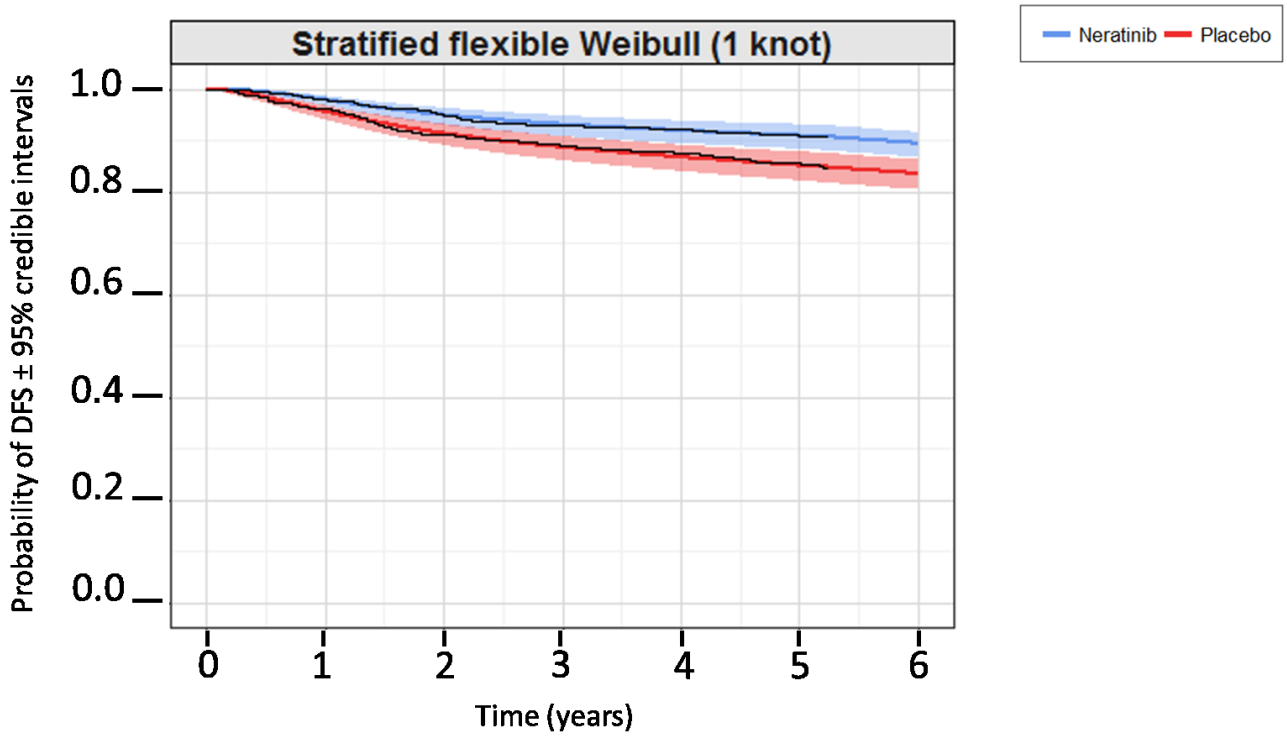


Figure L15E

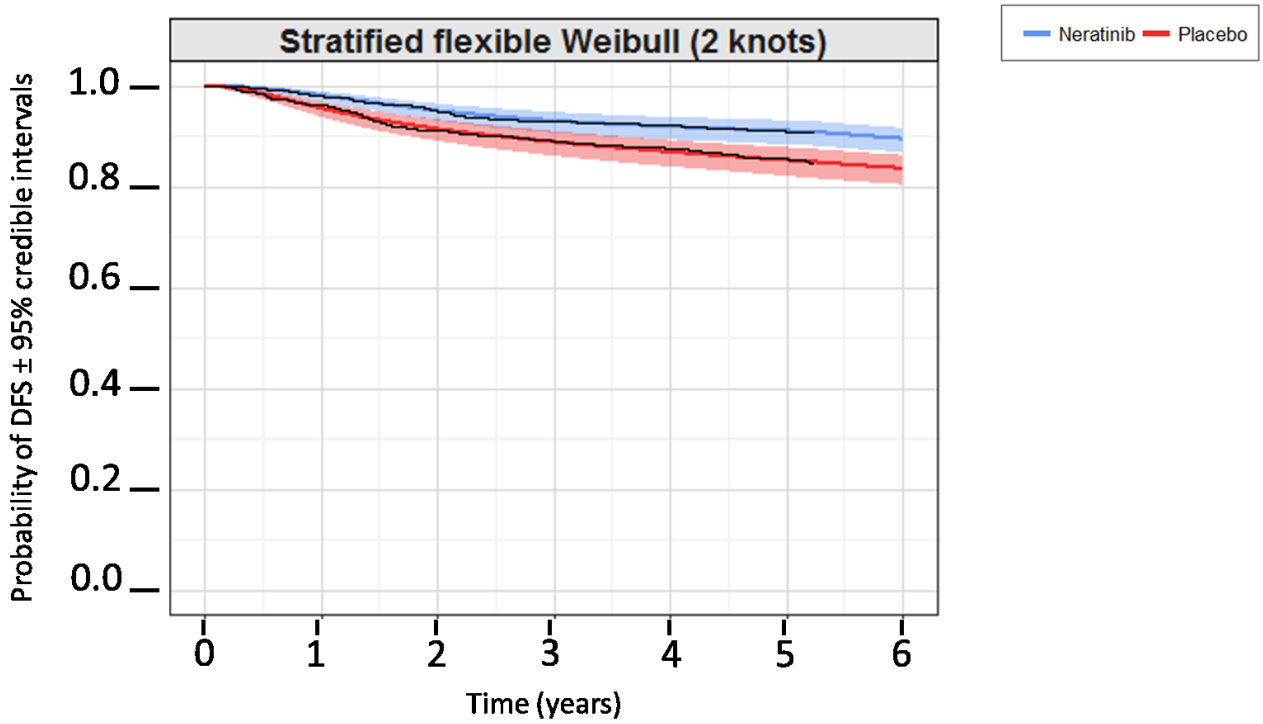
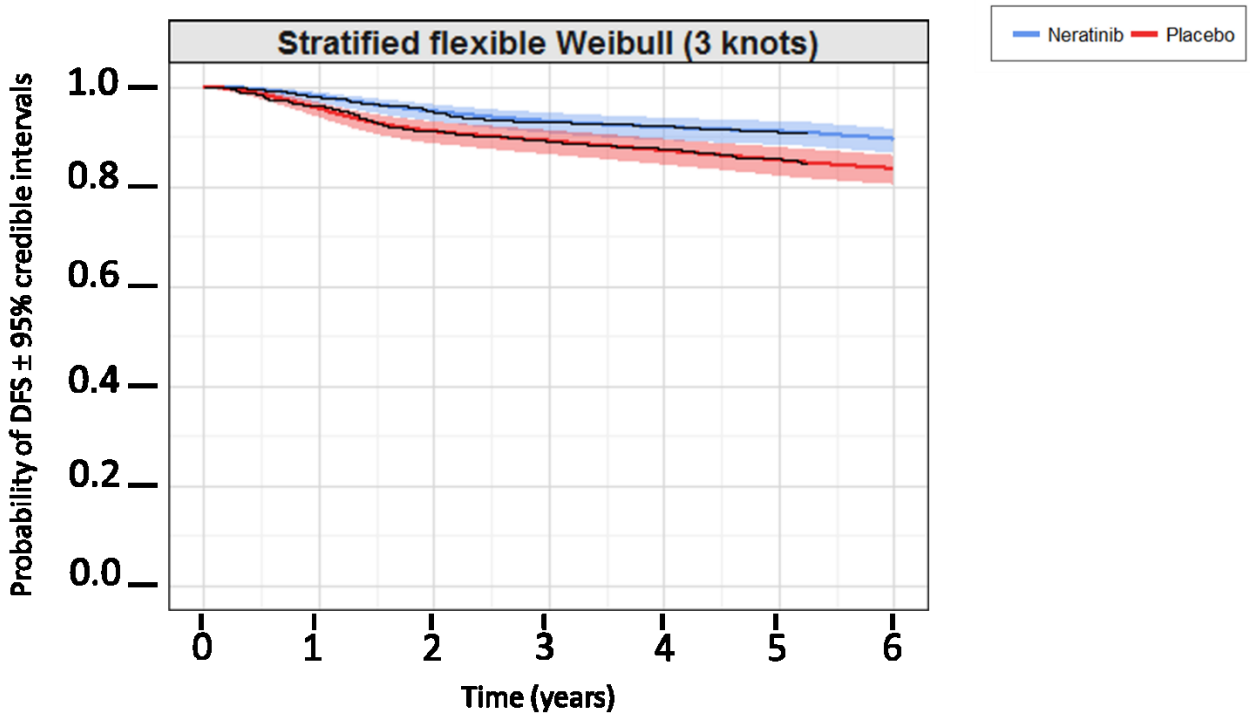


Figure L15F



a. **Please explain why the "generalised gamma did not appear to fit the data well at the end of the trial follow-up and therefore may not produce accurate extrapolations beyond the clinical trial data".**

As can be seen in Figure L14J above, at the end of the trial follow-up for EXTENET the generalised gamma underestimated the Kaplan-Meier (KM) curve for the neratinib arm, and overestimated the placebo arm (compared with the KM data). The good statistical fit is, thus, likely to result from a good fit to the early part of the trial data. As such, extrapolations based on the generalised gamma are likely to result in overpredictions of placebo and underprediction of neratinib survival long-term. Further, from examining all distributions fitted, generalised gamma is a clear outlier towards the end of the trial follow-up with the poorest visual fit to the later part of the KM data for both arms.

b. Based on the results presented in Section L.6.1.1 of Appendix L, please include the generalised gamma as an option to parametrise iDFS in the model.

This has been added as a selection option for the model. However, as outlined in response to a), generalised gamma should be considered an outlier of the distributions fitted to the data due to the poor visual fit to the KM curve towards the end of the trial. Therefore, Puma considers this to result in unrealistic predictions of the long-term survival.

Overall survival

B12. Parametric survival curves were fit to general population survival data, instead of using UK lifetables directly.

a. Please clarify why this was not directly sourced from UK lifetables.

The data used are taken from UK lifetables. To clarify the submission text, reconstructed patient-level data were created directly from UK lifetable data for 10,000 patients. This number was chosen to be small enough to allow the analyses to run at a reasonable speed while being large enough to capture the shape of the survival curve and be representative of the error.

Survival models were fitted to the data derived from the UK lifetables and predictions made from the distribution of the mean age in the trial. Using this approach instead of the lifetables was necessary for integrating the external evidence for iDFS into the

iDFS extrapolations. It also meant that predictions could be made corresponding to the cycle length of the model instead of 1-year intervals.

For consistency across scenarios, iDFS modelling (with and without use of external data) has been kept as the only data option in the model. Given the good fit of extrapolation to the simulated data it is expected that the results would be equivalent to using the lifetable data directly, but have the advantages mentioned above.

b. Please include in the model the option to use data directly from UK lifetables.

B13. Please provide an option (i.e. via drop-down menu selection) to run the model using the most recent OS data (cf. question A13).

As no more recent data are available (see Question A13) this change was not possible.

Recurrence

B14. On Page 101 in document B of the CS, it is mentioned that "it is not evident from comparing the 5-year data with the 2-year data cut that the proportion of site of recurrence varied over time; thus, proportions from the 5-year data were kept constant through the modelling time horizon". Please clarify how this is determined.

As shown in Tables 31 and 32 in Section B.3.3.3, the proportion of distant recurrence was 81.6% at 5 years and 80.0% at 2 years for neratinib and 69.2% at 5 years and 70.4% at 2 years for placebo. This similarity across the two time points of follow-up was the rationale for using a constant proportion over time. No further analyses were undertaken.

B15. Figure 36 in document B of the CS shows the post-distant recurrence survival stratified by year of recurrence from randomisation.

a. Please indicate the rationale for the following statements: "it is clear that patients with a recurrence within the first year since randomisation appear to have a poorer prognosis than those with a later recurrence.

However, there does not appear to be a clear differentiation between time categories of recurrence beyond the first year of ExteNET".

As stated in Document B, previous publications indicated that patients experiencing an early recurrence (within 12 months) could be anticipated to have worse outcomes than those patients experiencing a later recurrence. Thus, this was investigated as part of the model development. As can be seen in Figure 36 of Document B, patients in the ExteNET trial having a recurrence within 12 months had a statistically significantly shorter OS than those whose distant recurrence was later (P=0.0338). The base-case model therefore included stratification by time of post-distant recurrence (< 12 months and ≥ 12 months) and this was explored in a scenario analysis that indicated the inclusion of separate survival for distant recurrence is the conservative assumption (Scenario 6).

b. Based on Figure 36, it may be argued that 36+ have a better prognosis than the rest. If that is the case, please include this category in the model as well.

The available data are immature and there are few reported events in the 36+ subgroup. Given these limitations it would be questionable if this analysis would be informative and analyses of current data did not show the survival for this subgroup to be significantly different (*P* = 0.17). Therefore, this option has not been included in the model. For reference, should this analysis have been feasible, including the 36+ months with a better prognosis would be beneficial to neratinib, so the current model reflects a conservative assumption here.

Remission

B16. Priority question: Please explain the main differences between the DFS and remission health states in the model. In particular, please indicate why patients in these health states are assumed to have the same utility but patients in remission have a higher risk of transitioning to distant recurrence and, therefore, to die.

This is covered in Section B.3.4.5. "In the base case, utility in the remission state was assumed equal to 'disease free,' as these health states are generalisable because the patients are disease free in both. A similar assumption has been made

in the pertuzumab appraisal (ID1192) for adjuvant treatment of early HER2+ breast cancer and in a neoadjuvant setting (TA424)."

The implication from the question is that the utility of a patient in iDFS or remission would in some way be dependent on their risk of transition to distant recurrence and subsequently to dead. We are unaware of any evidence to support this assumption in an appropriate population and, therefore, view the assumption in the submission as appropriate given the justification provided. Further, the neratinib arm has a higher proportion of patients with distant recurrence and, therefore, this is a conservative assumption as further utility decrements would affect the placebo arm to a greater extent.

B17. A monthly transition probability of 0.00757 for transitioning from remission to distant recurrence has been used, the same probability used in ID1192 and TA424.

a. Please justify why this was included in the current analysis and assumed to be constant with time.

The inclusion of the monthly transition probability data is justified as the appropriate data were not available from the ExteNET trial. Transitions from remission to distant recurrence were not followed in the ExteNET trial and, in total, [redacted] within 5 years follow-up. Therefore, the probability agreed to be most appropriate in ID1192 and TA424 was used in this analysis. This is also aligned with the response to Question B3, that the clinical pathway postrecurrence for patients treated with neratinib would be aligned with that given to patients treated with pertuzumab.

b. Kindly compare the abovementioned probability with the transition probabilities that derived from the trial data from remission to distant recurrence, from iDFS to distant recurrence and from iDFS to local recurrence.

As data were not available from ExteNET to inform this transition probability a comparison cannot be presented.

Validation

B18. Priority question: Please provide details about what validation efforts were performed in Section B.3.10 of the company submission and the results of these validation efforts. This could be presented for example (but not necessarily) with the help of the validation tool AdViSHE (https://advishe.wordpress.com/author/advishe/).

Face validity and external validity steps are described in Section B.3.10 and refers to Section B.3.3.1 specifically in relation to the validation associated with iDFS. Given the importance of the iDFS extrapolation, the cross validation of alternative methods for extrapolation and the explicit use of long-term data within the extrapolation provides a key validation of the extrapolation and use of the primary endpoint from ExteNET in the model.

In addition, further validation steps were undertaken to assess internal validity and cross validity.

Internal validity was assessed using quality-control procedures for verification of input data and coding was performed by staff not involved in the model development and in accordance with a prespecified test plan. These procedures included verification of all input data with original sources and programming validation.

Verification of all input data was documented in the relevant worksheets of the model. Any discrepancies were discussed, and the model input data were updated where required.

Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications (Microsoft Corporation; Redmond, Washington) code.

With regard to cross-model validity, comparison of results with other models analysing the same treatments (i.e., cross validity) was sought where suitable models were available. However, this is, to our knowledge, the first economic evaluation undertaken for neratinib in the extended adjuvant treatment of adult patients with early-stage HR+, HER2-overexpressed/amplified breast cancer, and who are less than 1 year from the completion of prior adjuvant trastuzumab-based

therapy. Therefore, there are no published economic analyses with which to compare.

B19. Please provide values which can be used to validate the tails of the Markov traces obtained in the model. This could be presented for example in the form of a table comparing the expected survival probability at 10, 20, 30, 40, 50 years based on available data, literature or experts, and the same probabilities predicted by the model.

As presented in Section B.3.3.1, the longest available and most appropriate data for the UK (HERA, mean follow-up 11 years) have been used explicitly in scenario analysis in the economic model as well as for validation of the base-case extrapolation of iDFS. No relevant data with longer follow-up are to our knowledge available, thus, further long-term validation against external data cannot be added as requested. In addition, expert input sought from a clinical adviser confirmed that long-term survival reflective of current treatments is still unknown due to no long-term data being available. Therefore, validating based on time points 20, 30, 40, and 50 years would be speculative without appropriate data for reference.

Costs

B20. Priority question: In section B3.5.1.1 it is stated that although neratinib per the label should be given continually for 1 year, the actual mean treatment duration observed in ExteNET was 8.10 months, when treatment discontinuation was accounted for. Thus, treatment duration was set at 8.1 months in the model.

a. Please clarify whether this is based on the amount of neratinib dispensed in the trial or the amount patients reported taking.

Neither, it is the mean duration of treatment from the ExteNET study for the label population reflecting the time on treatment. The amount of neratinib taken by patients is captured in the dose intensity, covered in Question B21. As discussed during the clarification call, the ERG clarified that they wanted information about why the duration is shorter than the prescribed 12 months of treatment. This is because of treatment discontinuation due to, e.g. adverse events, subject request, and protocol violations, shortening the mean duration of treatment.

b. Kindly clarify whether this refers to the mean treatment duration based on the whole ExteNET study population or only the label population. If it is not calculated specific to the label population, please recalculate and include this option in the model (e.g. via drop-down menu selection).

We can confirm that the mean duration of treatment is based on the label population.

B21. Priority question: The relative actual dose intensity of [redacted]% was calculated from the ExteNET trial. Please clarify whether this is calculated based on the label population. If not, please recalculate according to the label population and include it in the model.

This can be confirmed as being calculated based on the label population in the ExteNET trial.

B22. Priority question: Please clarify whether the proportion of the label population who are expected to receive concomitant and subsequent endocrine therapy alongside neratinib or standard care is costed in the model. If not, please cost this in the model.

This has been added to the model.

B23. Section B3.6 states that the selection of subsequent treatments following recurrence which were included in model were obtained from the NICE appraisal of pertuzumab (ID1192).

a. Please provide details of how ID1192 identified and selected the list of treatments included in the model.

This is covered in Section B.3.5 in ID1192 and Section B3.6 in the current submission.

b. Please provide details of how the corresponding proportions of patients who would receive these different subsequent treatments in this population was calculated.

We have assumed that the question is related to how this was incorporated into the current model and not how it was incorporated into the ID1192 model. For the current model, the proportion of patients entering distant recurrence was multiplied by the proportion of each treatment in first line and a proportion of these would be

assumed to go on to receive second-line treatment (informed by expert clinical opinion). As data were not available to split first- and second-line metastatic treatment, the costs of first- and second-line treatment were applied to those entering distant recurrence. The values informing these calculations are provided in Table 52 of the submission and further explanation is provided in Section B.3.6.

B24. Expert opinion was used to identify subsequent treatments following recurrence and the likely shares of these different treatment options in clinical practice. The market shares estimated by expert opinion (Appendix M, Table 65) differ from those in the pertuzumab appraisal.

a. Please provide further justification for choosing the treatments and values from the pertuzumab appraisal over those obtained from expert opinion.

The rationale for choosing the values used in the pertuzumab appraisal over those obtained from expert opinion was for consistency across the two appraisals. As clarified in response to earlier questions, Puma believes that the treatment pathway following recurrence for neratinib- and Pertuzumab-treated patients should be similar and, thus, also the subsequent treatments received. This was confirmed by input from the clinical expert and, therefore, the values from the pertuzumab appraisal were selected for data to be consistent between appraisals. Those proportions of subsequent treatments were also agreed to be reflective of clinical practice by the ERG and the committee in ID1192. Given that only one clinician provided input to Puma we believe the values from ID1192 to have been more broadly validated and, as noted earlier, keep the appraisals consistent.

b. Please provide an option in the model to choose between these alternative sets of values.

The answer provided to part a of this question provides an explanation for the inclusion of one set of values in the analysis and, given this, no change has been made to the model.

Adverse Events

B25. Priority question: Please clarify whether the diarrhoea incidence and mean number of events included in the model (Table 37 in document B of the CS) is specific to the label population. If not, please present tables with values for the label population and include these changes in the model.

Yes, we can confirm the data used from ExteNET are for the label population, while data from CONTROL are for the ITT population (see Question B4 for further details).

B26. Priority question: Please clarify whether the calculation of the incidence and mean number of events of diarrhoea for patients receiving neratinib without prophylaxis limited to those in the ExteNET label population who did not receive loperamide. If not, please provide a calculation based on this group and include an option for this scenario in the model.

Following clarification, the ERG stated that the question related to confirming whether the analysis was based on the label population receiving neratinib without prophylaxis in ExteNET.

Text relating to diarrhoea treatment in the ExteNET study is provided in Section B.2.10.2. In the ExteNET study no protocol mandated antidiarrheal treatment was specified and patients only received antidiarrheal medication with the onset of diarrhoea. Therefore, no patients in ExteNET received prophylaxis and patients in that study are considered to be receiving neratinib without prophylaxis. Protocol-mandated antidiarrheal prophylaxis was included in the CONTROL trial and is the prophylaxis comparison made to the ExteNET data.

B27. Priority question: Please explain how the CONTROL data are used in the estimation of diarrhoea incidence and number of events in the model.

a. Please clarify whether the sample used matches the label population.

The data from CONTROL used in the model analysis refers to the ITT population. No separate analysis for the label population was available from CONTROL and therefore we cannot recalculate the diarrhoea parameters as requested. However, the aim of the CONTROL study was to demonstrate that protocol-mandated

proactive (before onset of diarrhoea) prophylaxis reduced the incidence and duration of diarrhoea.

b. If the sample used does not match the label population, please recalculate diarrhoea-related parameters based on a sample that matches the label population.

There is no clinical rationale, that we are aware of, that would suggest the effect of diarrhoea prophylaxis would differ between the ITT and label populations. On this basis, it is our view that the data included in the model are valid and accurate.

B28. The mean number of events for diarrhoea grade 1/2 in neratinib patients without prophylaxis is given as 17.4 in Table 53 in document B of the CS. However, in the model, in sheet "input summary general" cell J107 this parameter is 14.62. Please indicate which value is correct and make any necessary changes to the model.

The value of 14.62 is correct, this is a typo in Table 53. The model makes an adjustment removing those diarrhoea events in patients with grade 3 from all grade diarrhoea, to avoid double counting. It was noted when addressing this error that the incorrect value for patients "with prophylaxis" was provided in Table 53; this value reported as 5.1 should have been 3.5 ("input summary general" cell J108). These changes had a negligible effect on the results.

Utilities

B29. Priority question: In contrast to the analysis of iDFS, the analysis of the EQ-5D data was not restricted to the label population. Please provide the results of an analysis of the EQ-5D data that pertains to the label population and also provide an option (i.e. via drop-down menu selection) in the model to run it using these label population-specific utilities.

There may have been some confusion as the EQ-5D analysis conducted as part of the trial was conducted as a comparison between arms over time (see Sections B2 and B.3.4.1). This analysis does not provide values that could be used in the utility analysis and, therefore, a subsequent analysis using the label population was used to provide a utility estimate for iDFS (see Section B.3.4.5). EQ-5D data submitted

and used in the analysis were based on the label iDFS population. Given this, there is no need for a change in the model.

B30. Priority question: In the CS, various sources for the utility inputs have been used. The estimated utilities for disease-free and remission (using data from ExteNET) seem relatively high in comparison to the estimates from Lidgren et al. 2007.

a. Please provide justification for the choices made in the selection of sources for the utility inputs.

This is covered in Section B.3.4.5 of the submission. “Owing to utility data for both local and distant recurrence not being available from the ExteNET study, these values were obtained from the literature: Lidgren et al. (2007) for local recurrence and Lloyd et al. (2006) for distant recurrence. Both publications are well-established sources of utility data that have be used in previous NICE technology appraisals, including TA424 and ID1192.” and “In the scenario analysis, a single source Lidgren et al. (2007) is used to provide consistency across all health states, removing potential effects of mixing data sources.”

b. Kindly indicate to what extent the estimated utilities for disease-free and remission are valid and representative of these health states, and provide any known underlying reasons as to why these estimates differ from those in other sources.

This is covered in Section B.3.4.5 of the submission. “In the base case, utility in the remission state was assumed equal to ‘disease free,’ as these health states are generalisable because the patients are disease free in both. A similar assumption has been made in the pertuzumab appraisal (ID1192) for adjuvant treatment of early HER2+ breast cancer and in a neoadjuvant setting (TA424).” The estimate for iDFS in the ExteNET label population closely reflects the utility of the iDFS off treatment in ID1192, a comparable population. Variation in estimates across utility studies may occur for a wide number of reasons and this is the rationale for including alternative values in a scenario analysis.

B31. Priority question: Please provide all the available utility data from ExteNET for all health states, including the (minimal) data on utilities after recurrence (available from 11 patients).

Regarding the utilities after recurrence, please clarify whether these pertain to either local or distant recurrences.

In the label population, utilities were available for a total of 11 patients who experienced a recurrence and, of those, 8 patients experienced distant recurrence and 3 had local recurrence at the visit for the utilities. Given the small number of patients, applying the mixed-model analysis to these data, as was the case for iDFS, was not appropriate and therefore descriptive statistics have been included.

The utility values are based on the recurrence status (health state) of the patients at the time point of the administration of the EQ-5D:

[redacted]

It should be noted that, given the small sample size there is a high degree of uncertainty associated with the local and distant recurrence utility estimates as indicated by the range of values and standard deviation.

Section C: Textual clarification and additional points

C1. Priority question: Please amend the following issues detected in the economic model:

a. **On the "AEs" sheet if you select the "Neratinib without prophylaxis" option in the drop-down box over cell D23, the model does not generate an ICER in the "CE Results" sheet. Also, in sheet "Markov Int", cells BD19, BE19, BR19 and columns BL, BM and CL do not generate AE costs and QALY results. In sheet "Markov Comp" cells BD19, BE19, BO19 and columns BL, BM and CE also do not generate results. In sheet "Utility" cells F44 and F45 also stop calculating utility decrements associated with diarrhoea. The same error occurs when you select the "Exclude grade 1/ 2**

diarrhea" option from the drop-down box over cell D21 on the "AEs" sheet.

As discussed during the clarification call, we have not been able to replicate this issue, even after the ERG advised us of the version of Excel it uses, thus, we are unable to identify any error that needs to be corrected. If the ERG is unable to run the scenarios with these settings, Puma would be happy to provide alternative versions of the model preset with these selections if that could circumvent the issue.

b. **There is an error in the formula calculating disease free health state costs in sheet "Markov Int" column BV and "Markov comp" column BT. In "Markov Int" column BV the formula reads**

=IF(D18<5;'Input summary General'!$Y$54;'Input summary General'!$Y$55*F19)

This formula only multiplies the final section of the IF statement by the proportion of the cohort in the disease-free state, so in years 1-4 the full cost of the disease free state is applied, without weighting it according to the proportion of the cohort in that state. The formula should be amended as follows

=IF(D18<5;'Input summary General'!$Y$54;'Input summary General'!$Y$55)*F19

This change is also required in "Markov Comp" column BT

This issue has been addressed.

c. **In the "markov Int" sheet columns CC and CE, in the calculation of the monthly health state cost for distant recurrence it is unclear why the one-off cost is based on the proportion transitioning to distant recurrence in that cycle, while the monthly cost has been calculated based on the proportion of the cohort in the distant recurrence state from the previous cycle. The formula for column CC is as follows**

Cycle 5 (cell CC23) =(I23-I22)*'Input summary General'!$Y$61+(I23-(I23-I22))*'Input summary General'!$Y$60

The section highlighted in red causes the monthly health state cost to pertain to the proportion of the cohort in the distant state from the previous cycle. If this is a choice, please justify it, as for other health state costs the proportion from the current cycle is used. If this is an error, please correct columns CC and CE in "Markov Int" and columns BZ and CB in "Markov Comp".

This issue has been addressed.

d. The Reset button does not restore all defaults.

This issue has been addressed.

C2. Please check the table of contents in the appendices, as the pages do not correctly line up.

We assume this must be a Microsoft Word compatibility issue caused by the missing PRISMA diagram in your version referred to in Question B1. As the pages are correct in our version sent to NICE on 5 February, 2019.

C3. Please indicate whether outcomes that were not reported regarding the quality assessment of ExteNET (see Table 13 in the company submission) could be identified.

In response to the quality-assessment question, "Is there any evidence to suggest that the authors measured more outcomes than they reported?" (Document B, Table 13), the response given is "no", showing that all measured outcomes were reported. This is further expanded in Table 27 of Appendix D, where we state, "All measurements listed in methods were reported." There are therefore no unreported outcomes to identify.

C4. Please clarify whether data from HERA have been used in the base-case. Text on page 96 in document B of the CS and the electronic model suggests that they were not used as opposed to what is suggested in Table 30.

The HERA data were not included in the base-case analysis. The text on page 96 in Document B and Table 30 referred to the base case selected distributions used for the HERA data in the scenarios where this was used and not the base case cost-effectiveness analysis.

C5. Please clarify in what way the use of partitioned survival models has been critiqued by the NICE Decision Support Unit (DSU) as mentioned in page 86 in document B of the CS.

Please see the DSU report for their findings and discussion.

C6. Please explain how to interpret Figure 8 in Appendix L.

Figure 8 in Appendix L simply shows that additional external data available would be used to inform the long-term extrapolation.

C7. On page 85 of the company submission it is mentioned that a total of 21 economic evaluation studies were identified, including 5 health technology assessment (HTA) submissions. However, only 4 are shown in Table 28. Please clarify this and provide the missing details, if needed.

This is a typo and should have been “including four health technology assessment (HTA) submissions”.

References

Martin M, Holmes FA, Ejlertsen B, Delaloge S, Moy B, Iwata H, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017 Dec;18(12):1688-700.

Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012 Apr 18;(4):CD006243.

NICE. Early and locally advanced breast cancer: diagnosis and management. NICE guideline [NG101]. National Institute for Health and Care Excellence; July 2018. Available at: https://www.nice.org.uk/guidance/ng101. Accessed August 20, 2018

Von Minckwitz G, Procter M, De Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early her2-positive breast cancer. N Engl J Med. 2017;377(2):122-31.

Question and Clarification from ERG

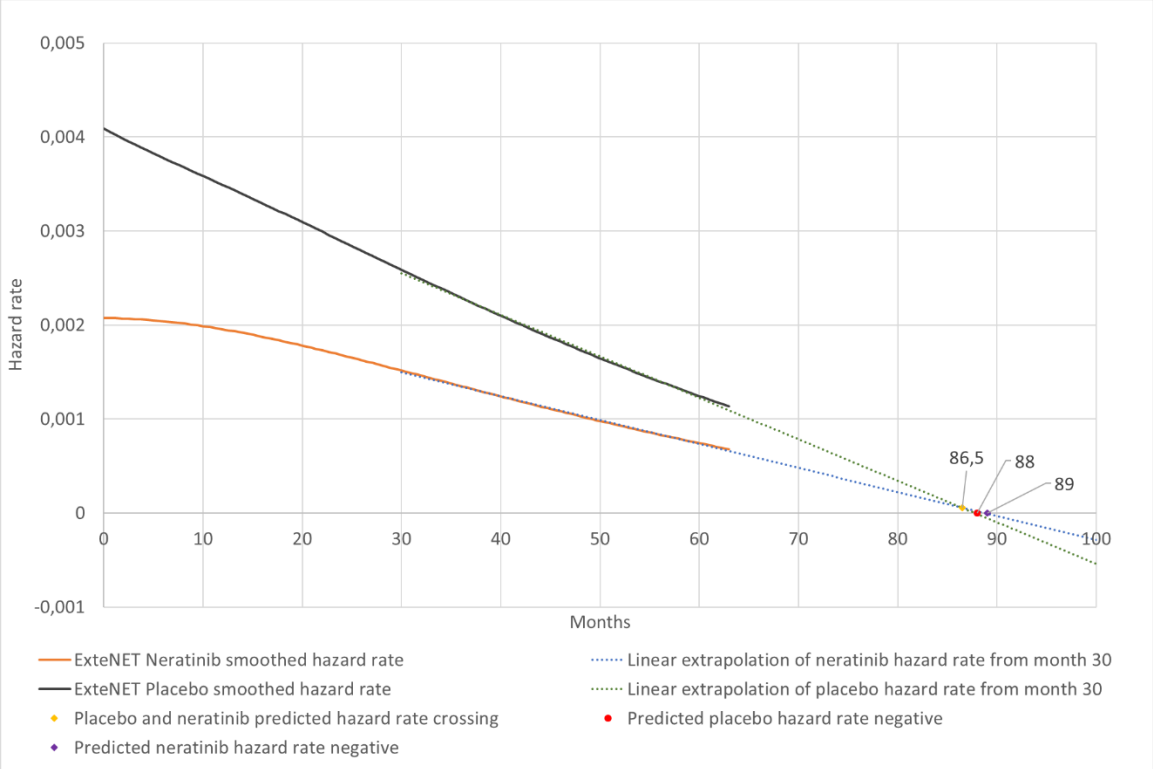
The purpose of this question is to see whether the curves cross at some point in time. This crossing point could be used as an estimate for the duration of the treatment effect. We know the company provided an extrapolation of the hazard ratio (which can be used to estimate the duration of the treatment effect too) but we want to see the extrapolated hazard rates just to confirm (or not) what we see with the hazard ratio (at first sight, it seems the hazard rates will cross before the extrapolated hazard ratio reaches 1). We are well aware of the limitations of the methodology but it is also true that in other parts of the submission similar limitations are faced. For example, the iDFS extrapolations used by the company resulted in implausible results (i.e. better survival than the general population) and yet it is used in the model and it is one of the main drivers of the results.

Puma response:

Based on the linear extrapolation requested by the ERG the lines will cross at approximately 86.5 months.

However, we would like to reiterate the response we previously provided as part of the clarification questions, and in our e-mail correspondence with NICE – that we believe such an extrapolation to be highly flawed and lacking in scientific rationale. To further clarify, we have provided additional information below.

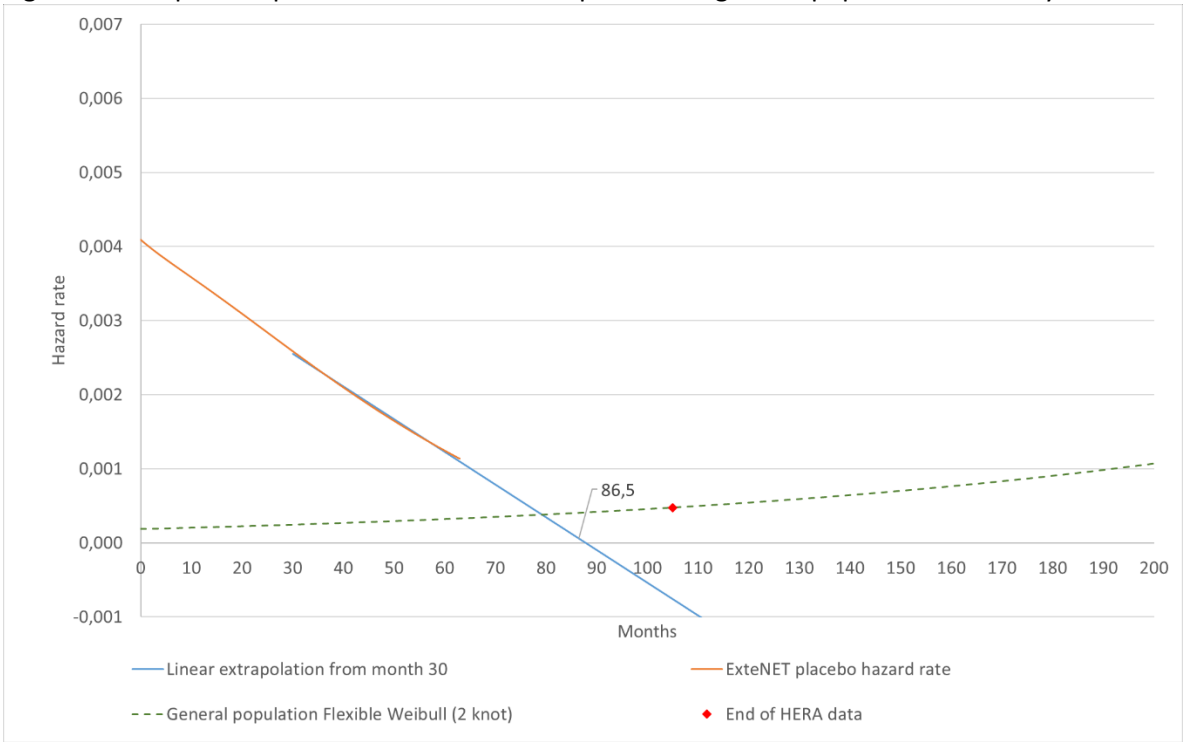
Figure 1. Linear extrapolation of smoothed hazard rate over time for neratinib and placebo



As can be seen from Figure 1, within 1.5 – 2.5 months of the arms crossing in the linear extrapolation, the hazard rates become negative and thus nonsensical. In the response from the ERG, they argued that they are aware of this limitation, but said that such limitations were also applicable to the company submission – due to extrapolations of iDFS survival crossing the general population survival. First of all we do not share the view that predicting a lower hazard compared to the general population is equivalent to predicting a negative risk of iDFS (which would essentially mean bringing patients back from the dead). Also as written in the company submission, clinical input sought by Puma and supported by the NICE appraisal of pertuzumab (ID1192) indicate that, given the curative intent of the treatment, it is plausible to assume that the iDFS risk would

approach that of the general population at some time point. Further, the crossing of iDFS and general population mortality has already been acknowledged in the company submission as well as accounted for in the modelling approach. This has been done by ensuring that patients cross over to general population mortality at the time this occurs in the model. This approach has been used and accepted in multiple previous appraisals. However, if we understand it correctly, this would not be accounted for in the approach proposed by the ERG. As clearly shown from Figure 2 the predicted hazard rate for the placebo arm using a linear extrapolation, results in the hazard rate being lower than the general population mortality before 86.5 months (when the extrapolated hazards from placebo and neratinib arms cross). Thus, the criterion of not predicting lower hazards than the general population would be violated if not accounted for by the ERG in their analysis. As presented in the company submission (section B3.3.1 Figure 30), the DFS hazards rate at the end of the HERA trial (equal to 8.5 years after initiation of neratinib treatment) are still higher for the HERA population compared with that of the general population. Thus, this further exemplifies the poor fit of a linear extrapolation of the hazard rates.

Figure 2: Extrapolated placebo hazard rates compared with general population mortality



However, our main overall criticism of the requested analyses is that, the ERG by performing such an analysis implicitly argues that a linear extrapolation of the hazard rates would provide a better iDFS prediction than that included as part of the company submission. We do not think it can be argued that a linear extrapolation of the hazard rates per arm is a valid method for predicting end of treatment effect, but is not valid for extrapolating iDFS – they are obviously interlinked. The extrapolation of iDFS in the company submission model (and thus the extrapolation of hazard rates) has been performed in alignment with the DSU guidelines as well as validated through recently published methods for survival extrapolation using external data. Unless the ERG has a scientific rationale for why using a linear extrapolation of the hazard rates would be superior to the methods already included in the submission, we strongly question the use of this method. If linear extrapolation results in a better prediction of when treatment effect stops than the distributions already included in the company submission, linear extrapolation should also provide a superior fit to the trial data compared with other functions. If the linear extrapolation doesn't provide a good fit

to the data, it can’t be argued to appropriately predict hazards over time and thus when the treatment effect would diminish.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Neratinib for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab [ID981]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Breast Cancer Now and Breast Cancer Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Now is the UK's largest breast cancer charity, dedicated to funding ground-breaking research into the disease. Our ambition is that by 2050, everyone who develops breast cancer will live. We're bringing together all those affected by the disease to improve the way we prevent, detect, treat and stop breast cancer. And we're committed to working with the NHS and governments across the UK to ensure that breast cancer services are as good as they can be, and that breast cancer patients benefit from advances in research as quickly as possible. Our main sources of income are individual giving and corporate partnerships. In particular in 2016/17 we received £2.7 million of income from Pfizer for our Catalyst programme, which provides grants for research. A list of funding that we have received from the pharmaceutical industry is available on our website here. Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of clinical effectiveness of drugs. Breast Cancer Care is the only specialist UK-wide charity providing support for women, men, families and friends affected by breast cancer. Our free services include support over the phone with a nurse or someone who's been there, our welcoming online forums, reliable information and local group support. Every day, our care, support and information help thousands of people to find a way to live with, through and beyond breast cancerWe are funded by entirely by voluntary donations, this includes individual and corporate donations, corporate sponsorships, project grants and income generated from events. Breast Cancer Now and Breast Cancer Care will be merging on 1 April 2019.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	Breast Cancer Now and Breast Cancer Care utilise their various networks of supporters to gather information about patient experience.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of breast cancer will cause considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be shocking and in the longer-term, the fear of breast cancer returning or spreading to other parts of the body (typically the bone, lungs, liver and brain) where it becomes incurable can cause considerable stress for both the patients and their loved ones. Around a quarter of women quarter of with HER2 positive experience a recurrence.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Surgery is usually the first option for women with primary or early breast cancer, although in some cases neoadjuvant treatment will be used to reduce the size of the tumour prior to surgery. Surgery may be followed by radiotherapy and systemic treatment such as chemotherapy, targeted therapy or hormone therapy, depending on the type of breast cancer and the balance of risks and benefits. All treatments have side effects. Treatment with chemotherapy usually has a number of unpleasant side effects which can have a significant impact on everyday activities, ability to work, social life and relationships. Hormone therapy can also have unpleasant menopausal side effects that can make it difficult for women to complete the recommended course of therapy. Current targeted therapies for HER2 breast cancer tend to be well tolerated.

8. Is there an unmet need for patients with this condition?	Adjuvant treatments for patients with HER2 positive breast cancer are already in use. However, any treatment that improves outcomes is a welcome step forward for patients.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The main advantage of neratinib is the improvement in invasive disease free survival (IDFS), recurrence and distant recurrence at five years. The ExteNET trial demonstrated an absolute improvement in IDFS amongst those taking neratinib after adjuvant trastuzumab of 2.5% to 90.2% at five years compared to those that did not. There were also reductions in recurrence (local or regional invasive recurrence) of 1%, and distant recurrence of 2% amongst those taking neratinib. There was a relative reduction in the risk of recurrence and death of 33%. Whilst absolute improvements in IDFS are incremental to the current standard of care, much progress has been made in breast cancer over the years through incremental improvements. For example, the addition of a taxane to an anthracycline chemotherapy regime reduces the absolute risk of recurrence by 4.6% and of overall mortality by 3.2% at 8 years.[1] The use of aromatase inhibitors compared with tamoxifen in postmenopausal women reduces the absolute risk of recurrence by 3.6%, and overall mortality by 2.7% at 10 years.[2] Women with breast cancer and their families welcome any improvement in outcomes. Neratinib is taken orally and so patients do not need to travel to hospital except for monitoring purposes.

[1] Early Breast Cancer Trialists' Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. *Lancet* 2012; 379: 432-44. Available at: DOI: 10.1016/S0140-6736(11)61625-5.
[2] Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015; 386:1341-52. Available at: DOI 10.1016/S0140-6736(15)61074-1

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage of this technology is the side effects, and specifically diarrhoea. 95% of those taking neratinib in the ExteNET trial experienced diarrhoea (compared to 35% of those that did not); 43% of whom experienced grade 3 diarrhoea (compared to 2% of those that did not take neratinib). Diarrhoea can impact negatively on patients' quality of life. Intensive loperamide on development of symptoms can reduce rates of grade 3 diarrhoea, and trials are ongoing to assess the impact of proactive loperamide early in treatment with neratinib. One patient that we spoke with was given loperamide to take for diarrhoea with neratinib. This initially had the effect of making her constipated and the dose had to be reduced, but she now finds that any diarrhoea can be dealt with by a low dose of loperamide. The patients who responded to our survey did not experience diarrhoea or described their side effects as 'minimal'. One patient said that her experience taking neratinib was much better than she had anticipated. Taking neratinib does also extend treatment time by a year. In deciding whether to take neratinib patients will want to balance the extended treatment time, additional monitoring appointments, and likelihood of severe diarrhoea with the improvements in outcomes. One patient explained that as a younger woman with a child, whose partner had recently passed away, she felt that the benefits, and specifically the 50% relative reduction in risk of recurrence for women with her type of breast cancer (which is hormone receptor positive as well as HER2 positive), outweighed the extended treatment time, monthly hospital appointments and the side effects, which were under control, and that she was 'prepared to throw a lot' at preventing a recurrence of her breast cancer.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The marketing authorisation that has now been granted for neratinib by the EMA is for patients that are hormone receptor positive as well as HER2 positive, and have completed adjuvant trastuzumab therapy less than 1 year prior to starting treatment with neratinib. Subgroup analysis from the ExteNET trial suggested that these patients benefit more from extension of adjuvant treatment with neratinib. There was a relative reduction in the risk of recurrence in those with hormone positive breast cancer of nearly half (49%) and those that had completed adjuvant trastuzumab less than 1 year previously of 35%.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- A diagnosis of breast cancer can cause considerable anxiety to the patient as well as their family and friends, including the fear of it recurring or spreading to other parts of the body where it becomes incurable.
- Neratinib provides improvements in invasive disease free survival, and local and distant recurrence in women with HER2 positive early breast cancer. Improvements in outcomes are welcomed by women with breast cancer.
- Diarrhoea is a significant side effect of neratinib, which can have a negative impact on patient's quality of life. However, this can be controlled with anti-diarrhoeal medicines. Several patients we spoke with experienced minimal side effects on neratinib.
- Patients will need to consider the balance between the extended treatment time and associated hospital appointments, as well as the likelihood of experiencing side effects with the fact this is an oral treatment which can be taken at home, and the improvements in outcomes associated with neratinib. One patient that we spoke with believed the improved outcomes outweighed, for her, the diarrhoea, which was controlled, and additional hospital appointments.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Neratinib for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab [ID981]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UK Breast Cancer Group**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NHS funded tertiary cancer centre**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Extended adjuvant treatment for early HER2 positive breast cancer Clinical setting after completion of neoadjuvant and/or adjuvant HER2 targeted therapy and cytotoxic chemotherapy

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in invasive cancer free survival of 1.5% at 2 years and at 5 years
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Neoadjuvant or adjuvant cytotoxic chemotherapy with concurrent HER2 targeted therapy (Herceptin only or Herceptin plus pertuzumab) Adjuvant HER-2 targeted therapy (Herceptin only or Herceptin plus pertuzumab) for 12 months No current extended adjuvant HER2 targeted therapy regime beyond 12 months

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Trastuzumab for adjuvant treatment of early HER2 positive breast cancer [TA107] Pertuzumab for the adjuvant treatment of HER2 positive breast cancer [TA569] No current extended adjuvant HER2 targeted therapy regime beyond 12 months
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Differences of opinion between professionals across the NHS
• What impact would the technology have on the current pathway of care?	Extend pathway of care for high risk HER2 positive early breast cancer patients, predominately in hormone receptor positive, HER2 positive breast cancer
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not currently in use in NHS practice.
• How does healthcare resource use differ	Extended adjuvant HER2 targeted treatment for 1 year beyond standard adjuvant HER2 targeted therapy

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training clinical staff Out-patient capacity for extended adjuvant HER2 targeted treatment
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes ExteNET trial Lancet Oncology 2016; Invasive cancer free disease survival significant benefit at 2 years from randomisation in favour of neratinib (stratified hazard ratio 0.67, 95% CI 0.50–0.91; p=0.0091). The 2-year invasive disease-free survival rate was 93.9% (95% CI 92.4–95.2) in the neratinib group and 91.6% (90.0–93.0) in the placebo group. ExteNET trial Lancet Oncology 2017; significant invasive cancer free survival benefit after 5.2 years median follow-up (stratified hazard ratio 0.73, 95% CI 0.57–0.92, p=0.0083). . The 5-year invasive disease-free survival was 90.2% (95% CI 88.3–91.8) in the neratinib group and 87.7% (85.7–89.4) in the placebo group. Hypothesis generating potential clinical benefit in hormone receptor positive, HER2 positive breast cancer (HR 0.67, 95% CI 0.43- 0.83, 2 sided p value 0.063), which requires further follow-up data/ confirmatory trials. 10 year outcomes awaited Meta-analysis of HER2 dual blockade versus single agent HER2 therapy in the adjuvant setting shows clinical benefit (DeBiasi Frontiers in Oncology 2018) of dual blockade. However limited survival data for

	adjuvant neratinib limits scope of metaanalysis for this agent. Furthermore no data on impact of neratinib after neoadjuvant/ adjuvant pertuzumab or adjuvant trastuzumab emantisine.
• Do you expect the technology to increase length of life more than current care?	Yes, see comments above. The caveat would be that invasive cancer free survival is a surrogate endpoint, but there are limitations in gathering overall survival data in adjuvant trials in early breast cancer. Overall survival data for neratinib at 5 and 10 years is not available.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, by increasing invasive disease free survival and reducing morbidity caused by local and distant cancer relapse.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Hormone receptor positive, HER-2 positive early breast cancer show trend to benefit more from neratinib at 5 year follow-up, see previous comments. However further data/ investigatory studies required to confirm/ refute this hypothesis generating finding regarding clinical benefit. Patients where HER2 amplification and HER2 mutation are co-expressed may benefit from neratinib – hypothesis generating requiring additional data/ confirmatory studies (Coco Science Signalling 2018).
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical	Concomitant treatments – anti-diarrhoeal medication Additional cardiac monitoring tests – echocardiogram Additional clinic visits to assess for gastrointestinal / liver toxicity

implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
• Is the technology a 'step-change' in the management of the condition?	Patients and their families would be supportive of new technology which may reduce risk of invasive cancer recurrence after HER2 positive early breast cancer diagnosis and standard neo/adjuvant treatment.
• Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Significant gastrointestinal toxicity (diarrhoea) reported in the clinical trial Extenet where anti-diarrhoeal medication was not initially mandated. 'The most common grade 3–4 adverse events in patients in the neratinib group were diarrhoea (grade 3, n=561 [40%] and grade 4, n=1 [<1%] *vs* grade 3, n=23 [2%] in the placebo group), vomiting (grade 3, n=47 [3%] *vs* n=5 [<1%]), and nausea (grade 3, n=26 [2%] *vs* n=2 [<1%]). QT prolongation occurred in 49 (3%) patients given neratinib and 93 (7%) patients given placebo, and decreases in left ventricular ejection fraction (≥grade 2) in 19 (1%) and 15 (1%) patients, respectively.'

	Anti-diarrhoeal medication and dose modification indicated to allow patient adherence to neratinib and to improve patient quality of life on extended adjuvant HER2 targeted therapy.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Invasive disease free survival – yes Distant disease free survival - yes Overall survival - no Adverse events - yes

	Long term neratinib related adverse events - yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Invasive disease free survival is a surrogate end-point which captures loco-regional and distant relapse. There is an accepted relationship between invasive disease free survival and overall survival, although the magnitude of the relationship is not known in this or other adjuvant HER2 targeted clinical trials. Overall survival data is not available, and therefore clinical decision making needs to utilise the available data; invasive disease free survival.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Limited real world data available in UK experience
Equality	

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to technology across different cancer centres
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Invasive disease free survival benefit from extended adjuvant neratinib with median 5.2 year follow up
- Potential superior benefit in selected groups eg hormone receptor positive, HER2 positive early breast cancer
- Gastrointestinal toxicity significant in clinical trial would need to be mitigated by robust anti-diarrhoeal regimen in specialist clinics
- Additional cardiac monitoring indicated
- Limited data on impact of neratinib after adjuvant pertuzumab or trastuzumab emantisine

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Neratinib for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab [ID981]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Ciara O'Brien**
2. Name of organisation	**UK Breast Cancer Group // The Christie Hospital NHS Foundation Trust**
3. Job title or position	**Consultant in Medical Oncology**

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Neratinib for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab [ID981]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by **Breast Cancer Now and Breast Cancer Care** and consequently I will not be submitting a personal statement.

Name: MELANIE STURTEVANT.....

Signed:.....

Date:22/05/2019 .....

.....

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Clinical expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Nigel Bundred**
2. Name of organisation	**Manchester University NHS Foundation Trust**

3. Job title or position	Professor of Surgical Oncology / Consultant Breast Surgeon, Greater Manchester CRN Cancer Lead
4. Are you (please tick all that apply):	**X** an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? **X** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of the treatment for this condition is to prevent distant spread, which inevitably leads to death from breast cancer in HER-2 positive breast cancers.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant response would be prevention of distant recurrence i.e. reduced metastases and improved overall survival
9. In your view, is there an unmet need for patients and	In my opinion there is an unmet need for patients who fail to respond to adjuvant Trastuzumab treatment and the direction of travel is to earlier treatment with two anti-HER-2 therapies, either sequentially or concurrently.

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	In the present time if a patient has a HER-2 positive breast cancer which is not treated with neoadjuvant treatment, but receives adjuvant chemotherapy and Herceptin, patients undergo that treatment, then if they are ER positive, would have endocrine therapy, but if they are ER negative then no further therapy is offered.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines are used in HER2 positive cancer treatment.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well-defined but a plethora of data emerging showing the benefit of dual agent anti-HER-2 therapy has led to differences of opinion as to the best option. Some clinicians would try and use neoadjuvant Trastuzumab and Pertuzumab, with chemotherapy before surgery in the majority of patients. Whilst others would not use it in node negative, less than 2cm, HER-2 positive cancers. In this latter group, who are mainly ER positive, there is a need for extra treatments.

• What impact would the technology have on the current pathway of care?	The current technology potentially could impact ER positive patients who undergo no neoadjuvant therapy and help prevent distant recurrence and improve overall survival. Importantly, the evidence for dual anti-HER-2 monoclonal antibodies benefiting ER positive cancers is somewhat limited and there is pre-clinical and clinical data that tyrosine kinase inhibitor, small molecule HER-2 inhibitors may be better in this population.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will not be used in the same way as current care in NHS clinical practice because currently we do not prescribe Neratinib as adjuvant therapy and arguably the trial should have been done with Neratinib concurrent with Trastuzumab as adjuvant therapy, rather than sequentially in this way, but nonetheless the data shows a benefit for it to be given sequentially after trastuzumab.
• How does healthcare resource use differ between the technology and current care?	No oral AntiHER2 therapy licenced in the adjuvant setting.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, specialist clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No extra investment other than the cost of the drug and antidiarrhoeal prophylactics.

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I expect the technology to provide clinically meaningful benefits compared with current care.
• Do you expect the technology to increase length of life more than current care?	Yes if used appropriately, I would expect the technology to increase length of life more than current care in this population.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes I would expect technology to increase health-related quality of life more than current care.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Although the data shows a benefit at five years for both ER negative and ER positive early breast cancer that is HER-2 positive, the largest benefit seems to be in the ER positive population and that is the group who have the greatest need for extra treatments after adjuvant Trastuzumab, or possibly even concurrently with adjuvant Trastuzumab.
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology will be no more difficult for patients or healthcare professionals than current care, however the practical implications are that prophylactic management for diarrhoea will be required in a number of these patients and managing the consequences of the drug therapy will be required, which may require more breast care nursing or clinical input.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The rules should state they should not get more than the standard treatment in the ExteNet trial, in which patients got 12 months of Neratinib after Trastuzumab. No treatment beyond this should be given.
16. Do you consider that the use of the technology will result in any substantial health-	There will be health-related benefits once the treatment has been administered and reduced relapse rate and deaths from breast cancer.

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The technology is innovative in its potential to make a significant and substantial impact on health-related benefits over a five year period.
• Is the technology a 'step-change' in the management of the condition?	In so much as it is a new anti-HER-2 drug that works in the adjuvant setting, it is a step-change in technology, but there are several of these drugs, for which some evidence exists of their benefit but costs and the absolute benefit differ.
• Does the use of the technology address any particular unmet need of the patient population?	The technology addresses a particular unmet need in the ER positive, HER-2 positive patients who have undergone Trastuzumab and chemotherapy and are then commencing all adjuvant therapy.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Anti-diarrhoeal agents will be required to manage side effects.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials and technology were carried out partly in the UK so they do reflect current UK clinical practice.
• If not, how could the results be extrapolated to the UK setting?	The results could be extrapolated to the UK setting.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important finding is that Neratinib for 12 months significantly improved 2 year and 5 year invasive disease free survival in HER-2 positive early breast cancer after chemotherapy and Trastuzumab adjuvant therapy. Since the improvement was maintained at five years, one can assume that this will pan out in the population as a whole.
• If surrogate outcome measures were used, do they adequately predict	The surrogate outcome was disease free survival, but that's very closely related to overall survival in this population.

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Diarrhoea was noticed in the clinical trial, as was rash. Diarrhoea will have to be dealt with by anti-diarrhoea agents, but these are relatively cheap.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. How do data on real-world experience compare with the trial data?	Real-world data is limited with this drug, apart from the fact that subsequent studies have shown that diarrhoea can be managed with appropriate drug therapy.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.

22b. Consider whether these issues are different from issues with current care and why.	No.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Neratinib given for one year after one year of adjuvant Trastuzumab in HER-2 positive breast cancer patients improves 2 and 5-year disease free survival.
- This is an additional agent which is orally administered and is a pan-HER inhibitor.
- The HER-2 drug market is becoming crowded and complicated, but Neratinib would be an important addition.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Neratinib (NERLYNX®) for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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None.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker and Dhwani Shah acted as a systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Dhwani Shah, Hannah Penton, Pim Wetzelaer, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Disclaimer

The cost-effectiveness results presented in this report are based on an electronic model that include a small error that was discovered after the report was submitted. This error has a negligible effect on the cost-effectiveness results. In particular, after correcting this error, the incremental cost-effectiveness ratio (ICER) in the ERG preferred base-case was increased by £83. Note also that all ICERs in this report will be superseded, since a Patient Access Scheme for neratinib was agreed.

Abbreviations

ACS	American Cancer Society
AE	Adverse events
AIC	Akaike information criterion
AiC	Academic in confidence
BIC	Bayesian information criterion
bid	twice daily
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CASP	Critical Appraisal Skills Programme
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CG	Clinical guidance
CI	Confidence interval
CiC	Commercial in confidence
CNS	Central nervous system
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
DATECAN	Definition for the Assessment of Time-to-event Endpoints in CANcer trials
DDFS	Distant disease-free survival
DFS	Disease-free survival
DFS-DCIS	Disease-free survival including ductal carcinoma in situ
DSU	Decision Support Unit
EED	Economic Evaluations Database
eMIT	Electronic Market Information Tool
EQ-5D	European Quality of Life-5 dimensions
EQ-5D-3L	European Quality of Life-5 dimensions-3 level
EQ-5D-5L	European Quality of Life-5 dimensions-5 level
ER-	Oestrogen receptor-negative
ER+	Oestrogen receptor-positive
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
ExteNET	Extended Adjuvant Treatment of Breast Cancer With Neratinib
FAC	Factual accuracy check
FACT-B	Functional Assessment of Cancer Therapy-Breast
GP	General practitioner
HAS	Haute Autorité de Santé
HER2+	Human epidermal growth factor receptor 2-positive
HERA	HERceptin Adjuvant
HR	Hazard ratio
HR	Hormone receptor
HR-	Hormone receptor-negative (oestrogen receptor-negative and progesterone receptor-negative)
HR+	Hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive)
HRQoL	Health-related quality of life
HTA	Health technology assessment
IBS	Integrated Brier score
ICER	Incremental cost effectiveness ratio

iDFS	Invasive disease-free survival
Incr.	Incremental
IQR	Interquartile range
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LYG	Life-years gained
M	Metastasis
MeSH	Medical subject headings
mg	Milligram
MUGA	Multigated acquisition
NA	Not applicable
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PDRS	Post-distant recurrence survival
PR-	Progesterone receptor-negative
PR+	Progesterone receptor-positive
PRESS	Peer Review of Electronic Search Strategies
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
q4h	Once every four hours
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SC	Subcutaneous
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STA	Single technology appraisal
UK	United Kingdom
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
tid	Three times a day
TNM	Tumour-node-metastasis
TP	Transition probability
TTDR	Time to distant recurrence
UK	United Kingdom
USA	United States of America
WTP	Willingness-to-pay

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1. Summary

1.1 Critique of the decision problem in the company's submission

The population addressed in the company submission (CS) is in line with the scope, i.e. includes patients with early hormone receptor-positive (HR+), human epidermal growth factor receptor 2-positive (HER2+) breast cancer who have completed a course of adjuvant trastuzumab less than one year ago. The intention-to-treat (all patients randomised into the study) as well as the safety population (all patients who received at least one dose of the study drug), are reported. Participants receive either treatment including neratinib or a comparator treatment. In line with the scope, the comparator includes participants receiving standard treatment and placebo.

The final scope prepared by the National Institute for Health and Care Excellence (NICE) defined four outcomes of interest: overall survival (OS), disease-free survival (DFS), adverse effects of treatment, and health-related quality of life. Subsequently, the CS included DFS (which included invasive disease-free survival (iDFS), disease-free survival including ductal carcinoma in situ (DFS-DCIS) and distant DFS (DDFS)), cumulative incidence of central nervous system (CNS) recurrence, time to distant recurrence (TTDR), adverse effects of treatment, and health-related quality of life (HRQoL).

The primary outcome in the ExteNET trial (the main trial presented in the CS) was iDFS while DFS-DCIS, DDFS, CNS recurrence, TTDR, OS, adverse effects of treatment, and health-related quality of life were secondary outcomes.

It should be noted that the definition the company used for iDFS pre-dated and was narrower than the standard definition. The CS defines iDFS as *"time from randomisation to the first occurrence of the following events: invasive ipsilateral breast tumour recurrence, local/regional invasive recurrence, distant recurrence, death from any cause, or invasive contralateral breast cancer"*. In contrast, the definition of iDFS in the guidelines by the DATECAN (Definition for the Assessment of Time-to-event Endpoints in CANcer trials) in addition to the aforementioned definition used by the company also included:

1. other causes of death (from breast cancer, from non-breast cancer cause, related to protocol treatment, from unknown cause),
2. progression of invasive ipsilateral breast tumour, local invasive progression, and regional invasive progression,
3. appearance or occurrence of metastases, or
4. second primary invasive cancer (non-breast cancer).

Given the narrower definition, iDFS events might have been missed in both arms of the ExteNET trial.

1.2 Summary of the key issues in the clinical effectiveness evidence

The CS comprised of a systematic review of the evidence for neratinib for the treatment of early HR+, HER2+ breast cancer after adjuvant trastuzumab. The CS and response to clarification provided sufficient details for the Evidence Review Group (ERG) to appraise the literature searches.

The company submitted evidence from two trials, ExteNET and CONTROL.

ExteNET was a phase III randomised control trial (RCT) which compared extended adjuvant therapy with neratinib versus placebo in people with HER2+ breast cancer (intention-to-treat (ITT)

population; neratinib n=1,420, placebo n=1,420), including patients with HR+/HER2+ breast cancer who are within one year of completing trastuzumab therapy (label population; neratinib n=670, placebo n=664). Table 1.1 provides an overview of the efficacy outcomes in the label population while Table 1.2 provides an overview of the safety outcomes in the label safety population.

Table 1.1: Overview of efficacy results of ExteNET trial (label population)

	Neratinib (n=670)	Placebo (n=664)	Effect estimate[a]
Estimated 2-year event free rates[b]			
DFS	NR[c]	NR[c]	NR[c]
iDFS	95.3%	90.8%	HR 0.49 (95% CI 0.30 to 0.78)
DFS-DCIS	95.3%	90.0%	HR 0.45 (95% CI 0.28 to 0.71)
CNS recurrence	0.34%	1.01%	NR
TTDR	96.3%	93.3%	HR 0.53 (95% CI 0.30 to 0.89)
DDFS	96.1%	92.9%	HR 0.53 (95% CI 0.31 to 0.88)
OS	NR[d]	NR[d]	NR[d]
Estimated 5-year event free rates[b]			
DFS	NR[c]	NR[c]	NR[c]
iDFS	90.8%	85.7%	HR 0.58 (95% CI 0.41 to 0.82)
DFS-DCIS	90.6%	84.8%	HR 0.55 (95% CI 0.39 to 0.77)
CNS recurrence	0.69%	2.09%	NR
TTDR	92.6%	88.2%	HR 0.58 (95% CI 0.39 to 0.85)
DDFS	92.4%	87.7%	HR 0.57 (95% CI 0.39 to 0.83)
OS	NR[d]	NR[d]	NR[d]
Health-related quality of life (HRQoL)			
HRQoL	NR[e]	NR[e]	NR[e]

Based on Tables 15 and 16 of the CS

[a] Unstratified Cox proportional hazards model; [b] Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported; c According to the CS, *"DFS includes iDFS, DFS-DCIS, and distant DFS, which were all outcomes in ExteNET"*; [d] OS data from ExteNET [redacted]; [e] Only reported in the ITT population. Although section B.3.4.1 of the CS suggests that results in the label population are available, relevant data were not available to the ERG

CI = confidence interval; CNS = central nervous system; CS = company submission; DDFS = distant disease-free survival; DFS = disease-free survival, DFS-DCIS = disease-free survival including ductal carcinoma in situ; ERG = Evidence Review Group; HR = hazard ratio; HRQoL = health-related quality of life; iDFS = invasive disease-free survival; ITT = intention-to-treat; NR = not reported; OS = overall survival; TTDR = time to distant recurrence

Table 1.2: Overview of safety results of ExteNET trial (label safety population)

	Neratinib (n=662)	Placebo (n=657)	Total (n=1,319)
Any TEAE	649 (98.0%)	567 (86.3%)	1,216 (92.2%)
Grade 3 or 4 TEAE	327 (49.4%)	76 (11.6%)	403 (30.6%)
Fatal TEAE	1 (0.2%)	0 (0.0%)	1 (0.1%)
Serious TEAE (SAE)	45 (6.8%)	36 (5.5%)	81 (6.1%)
Treatment-related TEAE	630 (95.2%)	360 (54.8%)	990 (75.1%)
Serious Treatment-related TEAE	19 (2.9%)	5 (0.8%)	24 (1.8%)
Diarrhoea (grade 1-2 TEAEs)	365 (55.1%)	213 (32.4%)	578 (43.8%)
Diarrhoea (grade 3-4 TEAEs)	261 (39.4%)[a]	7 (1.1%)[a]	268 (20.3%)[a]

Based on Tables 20 and 22 of the CS
[a] None classified as grade 4
AE = adverse event; CS = company submission; SAE = serious adverse event; TEAE = treatment-emergent adverse event

The company also presented results from a phase II, open label study safety and tolerability study, CONTROL, which investigated the effect of anti-diarrhoeal strategies on the incidence and duration of neratinib-associated diarrhoea, the most common side effect observed in the ExteNET trial (Table 1.3). The objective of this study was to characterise the duration, incidence and severity of diarrhoea in patients with early-stage HER2+ breast cancer with neratinib when administered with structured anti-diarrheal strategies after prior treatment with trastuzumab. Loperamide alone or in combination with budesonide or colestipol were tested. This is different from the ExteNET study, where antidiarrheal prophylaxis was not mandated by protocol and investigators were instructed to treat diarrhoea reactively at its earliest occurrence. It is unclear which of these approached best represents clinical practice, however, it should be noted that [redacted]

Table 1.3: Treatment-emergent diarrhoea in CONTROL compared with ExteNET

	Loperamide (n=137)	Budesonide + loperamide (n=64)	Colestipol + loperamide (n=120)	ExteNET neratinib arm[a] (n=1,408)
Median cumulative duration, days				
Any grade	14.0	24.0	16.0	59.0
Grade ≥ 2	5.0	6.0	3.5	10.0
Grade ≥ 3[b]	3.0	2.0	3.0	5.0[b]
Median diarrhoea episodes per patient				
Any grade	2	9	2.5	8
Grade ≥ 2	2	3	1	3
Grade ≥ 3	1	1	1	2[b]
Action taken, %				
Dose hold	15.3	18.8	9.2	33.9

	Loperamide (n=137)	Budesonide + loperamide (n=64)	Colestipol + loperamide (n=120)	ExteNET neratinib arm[a] (n=1,408)
Dose reduction	7.3	3.1	4.2	26.4
Discontinuation	20.4	10.9	1.7	16.8
Hospitalisation	1.5	0	0	1.4

Based on Table 25 of the CS
[a] loperamide as needed, safety population; [b] One grade 4 event in ExteNET safety population
CS = company submission

Where reported, efficacy outcomes favour participants in the neratinib group to participants in the placebo group. However, there are more (serious) adverse events, especially diarrhoea.

There are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. The safety data were predominantly derived from a Phase II, randomised, open label, active controlled study. As with many cytotoxic cancer drugs, the nature of the intervention precludes blinding; which can enhance bias. Key uncertainties in the evidence base relate to the use of iDFS as a surrogate endpoint for survival outcome (including the magnitude of benefit in survival) in the treatment of adjuvant treatment of breast cancer, and the generalisability of results of both trials to England and Wales.

1.3 Summary of the key issues in the cost effectiveness evidence

The structure of the conceptual model for this submission was similar to that taken in the NICE technology appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer (TA569). Concerns about the absence of OS data (per treatment arm) and the narrower definition used for iDFS, as discussed in the clinical effectiveness sections, also apply to the cost effectiveness model.

In the absence of treatment-specific OS data, the company assume the same mortality rate as the general population for the states of iDFS, local recurrence and remission. Only for the state of distant recurrence is the mortality rate higher. It is very likely that mortality rate has therefore been underestimated for those three states. Given that the difference between neratinib and standard care is in iDFS, this is likely to overestimate the life expectancy gain to neratinib. However, given the lack of OS data, the size of this bias is impossible to estimate.

There is uncertainty regarding the assumption of proportional hazards for iDFS. The selection of parametric models should have been broader and should have also included non-proportional hazards models. Regarding the treatment effect, the company assumed for the base-case analysis that the treatment effect observed at the end of the five-year follow-up was maintained until the patients had equal risk of an iDFS event as the general population. This implicitly means that there is a waning of the treatment effect starting at month 130 with a taper of effect over the next 3.83 years (month 176) at which point no further treatment effect is included in the model. The ERG does not agree with this choice and considers that a more rapid waning in the treatment effect is more plausible.

Post-distant recurrence survival (PDRS) analyses results in a poor fit in general and it is difficult to decide which distribution provides a better fit.

The incidence and mean number of events of diarrhoea with prophylaxis using loperamide was obtained from the safety population of the CONTROL trial. This population does not match the ExteNET label population in terms of length of time from trastuzumab or hormone receptor (HR) status. The company indicated that 73% of the CONTROL loperamide group matched the criteria for

the label population and that they were not aware of any clinical reason why the effect of diarrhoea prophylaxis would differ between the safety population of the CONTROL trial and the label population of ExteNET.

The ERG has concerns regarding the utility value obtained for the iDFS health state. This value was estimated using a generalised linear mixed model from a dataset that is incomplete and not fit for the purpose of the analysis (i.e. to obtain utility values for each health state in the model). As the company mentioned, any estimates derived from this analysis should be interpreted with caution due to the presence of cases with missing values. Although the issue with missing values was mentioned in relation to unexpected and counterintuitive results on the impact of different grades of diarrhoea on HRQoL, the same model and dataset were used to estimate the utility value for iDFS. The mixed models used by the company can accommodate missing values but only under the assumption that data is missing at random could the results be considered unbiased. That assumption might be questionable here (e.g. patients who are worst off are the first to stop filling in the EQ-5D (European Quality of Life-5 dimensions)). Therefore, similar concerns to those raised by the results for diarrhoea may also apply to the iDFS utility. The second concern regarding utilities is the possible impact of mixing data sources to estimate utility values for the other health states in the model, since these are not based on empirical data from the same study. Finally, since the overall utility of the general population is expected to decrease with time, the ERG considers it plausible to incorporate in the economic analysis an age-based decline in utilities.

The ERG also has concerns surrounding the calculation of treatment duration and relative actual dose intensity used in the model. In the company submission, it is stated that in the CONTROL trial, where prophylaxis was mandated alongside neratinib, diarrhoea related dose is maintained and dose reductions were lower than in the ExteNET trial, where prophylaxis was not mandated. Therefore, the ERG considers that the value for relative actual dose intensity ([redacted]%) and resulting treatment cost incorporated into the company base-case are likely to be lower than would be observed in clinical practice, if prophylaxis with loperamide is expected. The introduction of prophylaxis for diarrhoea may also be expected to reduce adverse events (AE)-related discontinuations. However, this was not observed in the comparison between the ExteNET and CONTROL discontinuation rates provided by the company, where the AE-related withdrawals in CONTROL were higher (which seems to contradict the results regarding AE-related dose reductions and holds).

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG preferred assumptions are described in detail in section 7.1.2 of this report and summarised below:

1. Implementing age-adjusted utility decline from Janssen and Szende 2014
2. Modelling iDFS according to a stratified generalised Gamma distribution
3. Declining treatment effect from month 63 (end of ExteNET follow-up) to month 140 (instead of considering it maintained)
4. Utility data for the iDFS health state from the ExteNET trial and from Lidgren et al. 2007 for the other health states
5. Neratinib dose intensity equal to [redacted]%

The cost effectiveness results of the ERG preferred base-case are presented in Table 1.4. The assumption with the largest impact on the ICER was the choice of the stratified generalised Gamma function to model iDFS. This resulted in an ICER increased by £9,660. All the other changes made by the ERG also resulted in increasing the ICER but in all cases the increase was less than £5,000. The

base-case ICER in the company submission was £24,585. The ICER based on the ERG preferred assumptions was £46,298.

Table 1.4: ICER resulting from ERG's preferred assumption

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Neratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Placebo	[redacted]	[redacted]	[redacted]				

ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALY = quality-adjusted life year

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

A probabilistic sensitivity analysis (PSA) and a one-way sensitivity analysis (OWSA) were also conducted using the ERG preferred base-case assumptions. The probabilistic ICER was £49,134, which was slightly higher than, but still in line with the deterministic ICER. Most of the simulations ([redacted]%) fell in the north-east quadrant of the CE (cost effectiveness)-plane. Standard care (placebo) dominated neratinib in the north-west quadrant of the CE-plane in [redacted]% of simulations. Neratinib dominated standard care (placebo) in [redacted]% of simulations in the south-east quadrant of the CE-plane. The cost effectiveness acceptability curve (CEAC) indicated that at willingness-to-pay (WTP) thresholds of £20,000 and £30,000, the probability that neratinib is cost effective is 7.9% and 22.5%, respectively. The results of the OWSA indicated that the disease-free health state utility value, relative actual dose intensity of neratinib and neratinib treatment duration have the largest impact on the ICER. However, the way the OWSA was conducted, allowing 10% variation from mean value for all parameters, seems arbitrary and may not represent an equally plausible range of variation for all input parameters. Whenever possible, the limits of (95%) confidence intervals should be used for each parameter to calculate the upper and lower bounds of any sensitivity analysis. Given the time constraints associated with this project, the ERG was not able correct this in the model. Therefore, the ERG considers that the OWSA based on 10% variation in input parameters should be interpreted with caution.

The ERG considered that the scenario analyses conducted by the company were insufficient to draw overall conclusions over the robustness of the model results. Therefore, the ERG conducted several additional scenario analyses to explore several sources of uncertainty that seem to be relevant for the model results identified by the ERG. From the results of these analyses it could be concluded that the ICER was most sensitive to changes in the selection of parametric survival curves for extrapolating of iDFS beyond the duration of the ExteNET trial (including the duration and type of treatment effect) and the assumptions about treatment durations and dose intensities for neratinib. Despite the ERG concerns regarding the utilities described in section 5.2.8, the impact of using different assumptions and values for utilities was not large. Therefore, it is possible that the uncertainties associated with the utilities (structural and input data uncertainty associated with the estimation of a generalised linear mixed model based on an incomplete dataset) are not captured in the current economic analyses. Other scenarios explored by the ERG considered alternative assumptions on the probability of transition from the remission health state to the distant recurrence health state, the proportions of patients with local recurrence, the costs associated to distant recurrence and the choice of different distributions for the extrapolation of PDRS. However, the impact on the results was minor compared to the previously described uncertainties. The cost effectiveness results of the ERG exploratory analyses are summarised in Table 1.5.

Table 1.5: Exploratory analyses undertaken by the ERG

Scenario	Section in main ERG report	Neratinib		Placebo		ICER £/QALY
		Costs	QALYs	Costs	QALYs	
Parametric distribution to model iDFS [and taper period in months]						
Stratified generalised gamma [77.02]*	7.2.2.1	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Stratified flexible Weibull (1 knot) [234.02]		[redacted]	[redacted]	[redacted]	[redacted]	£37,128
Flexible Weibull (1 knot) [113.02]		[redacted]	[redacted]	[redacted]	[redacted]	£38,178
Flexible Weibull (2 knots) [111.02]		[redacted]	[redacted]	[redacted]	[redacted]	£38,448
Generalised Gamma [76.02]		[redacted]	[redacted]	[redacted]	[redacted]	£80,818
Duration of the treatment effect (stratified generalised Gamma assumed for iDFS)						
Taper period of 0 months	7.2.2.2	[redacted]	[redacted]	[redacted]	[redacted]	£56,871
Taper period of 12 months		[redacted]	[redacted]	[redacted]	[redacted]	£54,175
Taper period of 24 months		[redacted]	[redacted]	[redacted]	[redacted]	£52,150
Taper period of 60 months		[redacted]	[redacted]	[redacted]	[redacted]	£47,785
Taper period of 77.02 months*		[redacted]	[redacted]	[redacted]	[redacted]	£46.298
Continued treatment effect		[redacted]	[redacted]	[redacted]	[redacted]	£42,392
Utilities						
ERG preferred base-case	7.2.2.3	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
No age-related utility		[redacted]	[redacted]	[redacted]	[redacted]	£42,050

Scenario	Section in main ERG report	Neratinib		Placebo		ICER £/QALY
		Costs	QALYs	Costs	QALYs	
decrement						
Utility set as in company base case		[redacted]	[redacted]	[redacted]	[redacted]	£43,848
Utility set from Lidgren et al. 2007		[redacted]	[redacted]	[redacted]	[redacted]	£50,912
Neratinib treatment duration and dose intensity						
ERG preferred base-case	7.2.2.4	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Dose intensity [redacted]%		[redacted]	[redacted]	[redacted]	[redacted]	£50,422
Dose intensity as in company base case ([redacted]%)		[redacted]	[redacted]	[redacted]	[redacted]	£42,168
Treatment duration of 12 months		[redacted]	[redacted]	[redacted]	[redacted]	£75,896
Treatment duration of 10.05 months		[redacted]	[redacted]	[redacted]	[redacted]	£61,265
Dose intensity [redacted]% + treatment duration of 12 months		[redacted]	[redacted]	[redacted]	[redacted]	£81,962
Transition probability form remission to distant recurrence						
ERG preferred base-case	7.2.2.5	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
TP = 0.3785%		[redacted]	[redacted]	[redacted]	[redacted]	£54,025
TP = 1.514%		[redacted]	[redacted]	[redacted]	[redacted]	£40,713
Proportions of patients with local recurrence						
ERG preferred base-case	7.2.2.6	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Neratinib: 13% local		[redacted]	[redacted]	[redacted]	[redacted]	£49,002
Neratinib:		[redacted]	[redacted]	[redacted]	[redacted]	£44,166

Scenario	Section in main ERG report	Neratinib		Placebo		ICER £/QALY
		Costs	QALYs	Costs	QALYs	
23% local						
Placebo: 26% local		[redacted]	[redacted]	[redacted]	[redacted]	£42,632
Placebo: 36% local		[redacted]	[redacted]	[redacted]	[redacted]	£51,001
Costs of distant recurrence						
ERG preferred base-case	7.2.2.7	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Cost of distant recurrence £200,000		[redacted]	[redacted]	[redacted]	[redacted]	£43,922
Cost of distant recurrence £150,000		[redacted]	[redacted]	[redacted]	[redacted]	£48,750
Parametric distribution to model PDRS						
Gompertz*	7.2.2.8	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Exponential		[redacted]	[redacted]	[redacted]	[redacted]	£48,415
Gamma		[redacted]	[redacted]	[redacted]	[redacted]	£46,331
Weibull		[redacted]	[redacted]	[redacted]	[redacted]	£47,738

* ERG preferred base-case

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, PDRS = post-distant recurrence survival; QALY = quality-adjusted life years; TP = transition probability

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company's submission provided sufficient details for the ERG to appraise the database searches, which were clearly presented, transparent and reproducible. An adequate number of databases were searched and a good range of additional searches were conducted for grey literature.

The company presented the first economic evaluation for neratinib in the extended adjuvant treatment of adult patients with early-stage HR+, HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab-based therapy. The model developed by the company was similar to the model developed for the appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer. The model includes relevant data on clinical effectiveness, adverse events, utilities and costs. Sensitivity (probabilistic and one-way) and scenario analyses were also performed.

1.6.2 Weaknesses and areas of uncertainty

A main area of uncertainty is the immaturity of the OS data for the label population. In request for clarification, the ERG asked for an interim analysis of OS to be conducted. In response, the company stated that due to amendment 13 this analysis was no longer going to be conducted. However, according to Table 6 of the CS, amendment 13 signifies an interim analysis at 124 events. Given that at the time of the ITT five-year analysis, 121 deaths had been reported across both treatment groups combined, the ERG believes an interim analysis of OS should have taken place for the CS.

There is uncertainty regarding the use of iDFS as a surrogate outcome measure of DFS and overall survival. The definition of this outcome was narrower than the standard definition of iDFS which included further events, as detailed before. Although this measure was used in a previous technology appraisal of pertuzumab (TA 569), the ERG did not comment on the validity of its use in this case. The implications of using this surrogate outcome for longer-term outcomes are unknown, which is a concern for the ERG. Additionally, the reliability of using a surrogate measure to inform estimates of overall survival is an important consideration, especially given that the direction of which it would influence the cost effectiveness evidence is unknown. However, it should be noted that some authors recently argued that iDFS could be a valid surrogate for OS (see section 4.2 for details).

There are concerns regarding the representativeness of the neratinib trial to the United Kingdom (UK) population. As stated by the company in their clarification response to question A11 (regarding further results on the label population of ExteNET), "*the number of UK patients is too small to perform an appropriate statistical test"*, which causes some concern to the ERG, especially as results reported for the ITT population differ between geographic regions (as discussed in section 4.2.3). Furthermore, none of the testing centres used in CONTROL were based in Europe which again raises concerns regarding the applicability of the findings to a UK population.

The clinical effectiveness concerns mentioned above also apply to the cost effectiveness analyses. Besides these, there is uncertainty regarding the assumption of proportional hazards for iDFS and the type and duration of the treatment effect. The ERG does not agree with the company's choices and considers that non-proportional hazards models and a waning in the treatment effect are more plausible.

Despite the ERG's concerns regarding the utilities (estimates for iDFS based on an incomplete dataset, combined with estimates for the other health states from various sources), the impact of using different assumptions and values for utilities was not large. Therefore, it is possible that the uncertainties associated with the utilities (structural and input data uncertainty associated with the estimation of a generalised linear mixed model based on an incomplete dataset) are not captured in the current economic analyses.

The ERG also has concerns surrounding the calculation of treatment duration and relative actual dose intensity used in the model. Since in the ExteNET trial prophylaxis was not mandated, the value for relative actual dose intensity ([redacted]%) and resulting treatment cost incorporated into the company base-case are likely to be lower than would be observed in clinical practice, if prophylaxis with loperamide is expected. The introduction of prophylaxis for diarrhoea may also be expected to reduce AE related discontinuations. However, this was not observed in the comparison between the ExteNET and CONTROL discontinuation rates provided by the company.

Finally, the scenario analyses conducted by the company were insufficient to draw overall conclusions on the robustness of the model results. The company should have considered a wider range of distributions to model iDFS. Assumptions regarding the type and duration of the neratinib

treatment effect, the source of utility data, the duration of neratinib treatment or the neratinib dose intensity should have been extensively explored.

2. Background

2.1 Introduction

In this report, the Evidence Review Group (ERG) provides a review of the provided evidence submitted by Puma Biotechnology in support of neratinib, trade name NERLYNX®, for treating early hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-positive breast cancer after completing adjuvant trastuzumab treatment in adult women.

2.2 Background and underlying health problem

In the company submission (CS),[1] the company identifies breast cancer to be the most common cancer in the United Kingdom (UK) among women according to the National Institute for Health and Care Excellence (NICE).[2] The American Cancer Society (ACS) describes breast cancer as a malignant tumour that originates in the breast tissue.[3] The company states UK mortality rates from breast cancer are the 14th highest in Europe.[1]

Breast cancers are distinguished by the tumour-node-metastasis (TNM) staging system and molecular biomarkers, which can be used to drive prognosis and treatment-related decisions.[3-5] Such molecular biomarkers include HR+, HER2+, oestrogen (ER+), or progesterone (PR+),[1] specifically ER+ and PR+ which can induce breast tissue growth or change as a response method to the changing hormone levels.[6, 7] The dominant driver to the development of breast cancer tumours is the over expression of the HER2 oncogene which can influence the metabolic functions of the tumour cells, enable cell survival, induce cell proliferation, and increase invasiveness.[8, 9] When patients have HR+/HER2+ breast cancer, this indicates the tumours co-express hormone receptors (HRs, which could be ER and/or PR) and HER2.[1] Such a co-expression then modifies the tumour response to both HER2-directed and hormonal therapies.[1]

The CS notes that the use of HER2-targeted trastuzumab for patients with early HER2+ breast cancer in the adjuvant setting has led to a reduction in the disease occurrence and improved overall survival (OS).[1] According to the HERception Adjuvant (HERA) trial, at a median follow-up of 11 years, women with HER2-positive early breast cancer after one year of adjuvant trastuzumab showed a 24% relative reduction in risk of a disease-free survival event, and a 26% relative reduction risk of death. The CS[1] further emphasises the prognosis for women with recurrent HR+/HER2+ breast cancer is poor due to most recurrences that develop typically involve incurable distant metastatic disease.[10, 11] Early breast cancer patients who experience a recurrence report the event as negatively impacting their health-related quality of life (HRQoL).[12, 13]

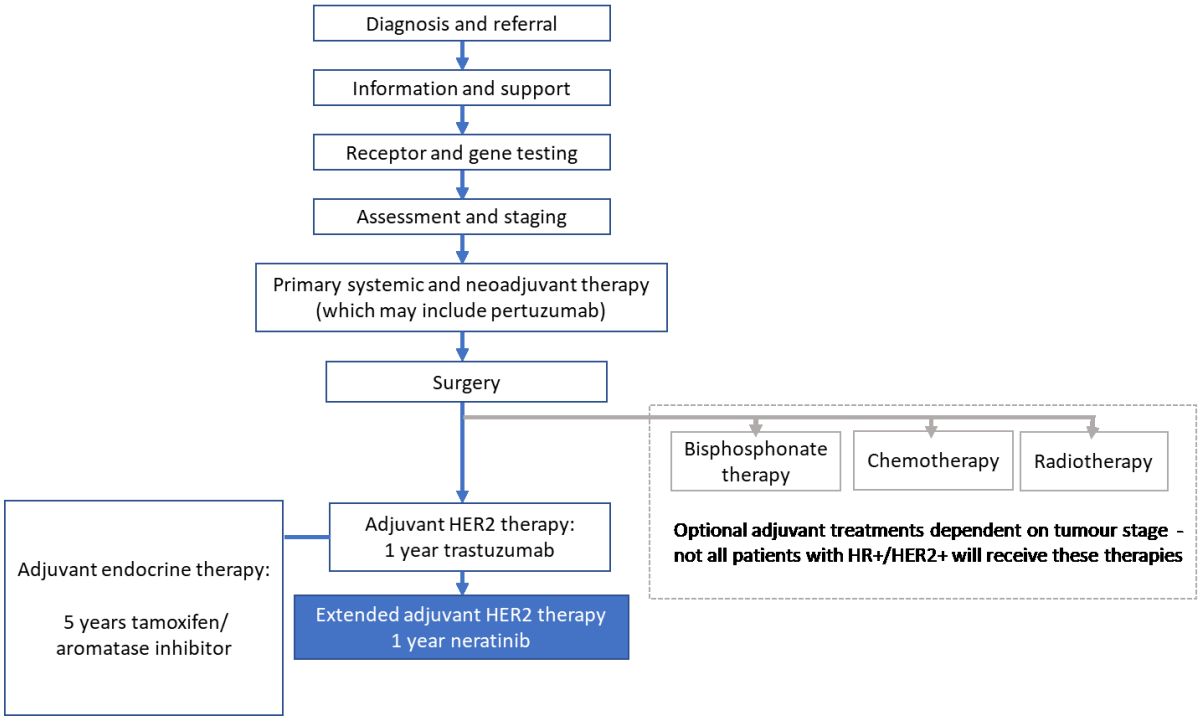
As identified in the clinical pathway of care in the CS, an early breast cancer diagnosis can be treated with curative intent.[1] After the type of breast cancer has been determined, the treatment generally involves surgery, supplemented with drug therapy, and radiotherapy. The aim of treatment for patients with secondary breast cancer is to control the further development and spread of the cancer, relieve symptoms, and maintain patient quality of life for as long as possible.[14]

The current standard of care in the National Health Service (NHS) for HER2+ breast cancer patients after surgery, chemotherapy, and radiotherapy, is a routine adjuvant therapy of three doses weekly of trastuzumab for one year.[1] Patients identified with HR+/HER2+ breast cancer will also receive adjuvant endocrine therapy, which can be in the form of tamoxifen or an aromatase inhibitor for five years, with the option to continue endocrine therapy beyond the original five years.[15]

Neratinib is identified as a HER2-directed treatment for early HR+/HER2 breast cancer patients for when patients have already received one year of adjuvant trastuzumab-based therapy.[1] This positioning in the treatment pathway is done in order to reduce the risk of disease recurrence.[1]

The company emphasises that at present within the UK NHS system, there are no treatment recommendations or approved HER2-directed therapies for patients with HR+/HER2+ breast cancer in the extended adjuvant setting after one year of treatment with trastuzumab-based therapy other than endocrine therapy.[1]

Figure 2.1: Neratinib: place in treatment pathway for early HR+/HER2+ breast cancer



Based on updated Figure 1 of the response to request for clarification[16]
HER2+ = human epidermal growth factor receptor 2-positive; HR+ = hormone receptor-positive

ERG comment: The CS suggested that the NICE clinical guidelines 101 recommend the use of adjuvant therapy and provide a simplified version of the NICE pathway (see Figure 2.1).[1] Furthermore, the company suggested that neratinib will be considered for patients with HR+/HER2+ breast cancer patients in the extended adjuvant setting (i.e. after patients receive one year of adjuvant treatment with trastuzumab therapy), therefore, no change is expected to the current recommended treatment pathway. The ERG agrees with this judgement in relation to the NICE guidelines.

Trastuzumab is recommended as an adjuvant treatment within the NICE guidelines, which state: *"Offer adjuvant trastuzumab for people with T1c and above HER2-positive invasive breast cancer, given at 3-week intervals for 1 year in combination with surgery, chemotherapy and radiotherapy as appropriate".*[15] Trastuzumab as a neoadjuvant therapy has not been evaluated by NICE. A licence extension for trastuzumab for HER2-positive early breast cancer patients was granted in 2012 to include neoadjuvant use in combination with chemotherapy followed by adjuvant therapy.

3. Critique of company's definition of decision problem

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE/ reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Patients with early HR+, HER2+ breast cancer who have completed a course of adjuvant trastuzumab less than 1 year ago.	As per the scope. The ITT population and safety population of the ExteNET and CONTROL trials will also be included in the evidence submission for completeness, which included all patients with HER2+ breast cancer regardless of HR status or time from completion of trastuzumab-based therapy. Early-stage breast cancer in the neratinib clinical trials included patients with stage I-III tumours.	The primary evidence supporting the submission does not differ from the NICE scope. For completeness, the ITT and safety populations of the neratinib clinical trials will provide supplementary efficacy and safety data from all participants who received neratinib.	No further comment.
Comparator(s)	Standard treatment with no further HER2-directed therapy.	As per the scope: no treatment, represented by the placebo arm of the ExteNET trial.	No treatment is consistent with the NICE scope.	Participants in the control arm receive standard treatment and placebo.
Outcomes	• OS • DFS • Adverse effects of treatment • Health-related quality of life.	As per the scope, including: • iDFS (2 years and 5 years) • DFS-DCIS • DDFS • Cumulative incidence of CNS recurrence • TTDR • Adverse effects of treatment • Health-related quality of life	DFS includes iDFS, DFS-DCIS, which were all outcomes in ExteNET. iDFS is the primary outcome of the ExteNET trial; DFS-DCIS, DDFS, CNS recurrence, and TTDR were secondary outcomes in ExteNET. OS data from ExteNET [redacted]	While the company emphasises iDFS as a primary endpoint, they use a definition that is not considered standard (see below). OS data not reported.

	Final scope issued by NICE/ reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			[redacted]	
Synthesis of evidence on health effects	Based on systematic review of published evidence.	As per the scope plus unpublished results of neratinib trials.	The ExteNET and CONTROL clinical trials are ongoing, so unpublished and recently published data are included that would not be captured by systematic review.	No further comment

Based on Table 2 of the CS[1]

CNS = central nervous system; CS = company submission; DDFS = distant disease-free survival; DFS = disease-free survival; DFS-DCIS = disease-free survival including ductal carcinoma in situ; HER2+ = human epidermal growth factor receptor 2-positive; HR+ = hormone receptor-positive; iDFS = invasive disease-free survival; ITT = intention-to-treat; OS = overall survival; TTDR = time to distant recurrence

3.1 Population

The patient population addressed by the company's statement of the decision problem matches that described in the final NICE scope. The patient population of interest is adults with early stage breast cancer who are HR+, HER2+ and have completed a course of adjuvant trastuzumab less than a year ago. Clinical evidence was available on this population (label population), which reflects the characteristics of the patient population in England who are eligible for treatment. The CS also presents the intention-to-treat (ITT) population and safety population of the ExteNET and CONTROL trials, which includes all patients with HER2+ regardless of HR status for completeness.

Pre-planned subgroup analyses, including nodal status and concurrent/sequential trastuzumab regimen, were also carried out as additional analyses for the label population and reported in the CS. However, nodal status was misclassified, i.e. patients with residual invasive disease in the breast but node-negative or unknown nodal status after neoadjuvant therapy were classified under the "1-3" positive node status.

3.2 Comparators

The NICE scope listed the sole comparator as standard treatment with no further HER2-directed therapy.[6] In the ExteNET trial, this is represented by the use of a placebo arm.[6]

3.3 Outcomes

The NICE scope identifies the outcomes to be overall survival (OS), disease-free survival (DFS), adverse effects of treatment, and health-related quality of life. For the ExteNET trial, DFS encompassed invasive disease-free survival (iDFS), disease-free survival including ductal carcinoma in situ (DFS-DCIS), and distant disease-free survival (DDFS).[6] The ExteNET trial used iDFS as the primary outcome and DFS-DCIS, DDFS, cumulative incidence of central nervous system (CNS) recurrence, time to distant recurrence (TTDR) as well as health-related quality of life (HRQoL) and adverse events as secondary outcomes.[6] OS results were not presented due to the OS data from the ExteNET trial not being available at the time of the CS: [redacted][6]

The definition the company used for iDFS was narrower than the standard definition (Table 3.2). Given the narrower definition, iDFS events might have been missed in both arms of the ExteNET trial.[17]

Table 3.2: Clinical events to be included in the definition of iDFS: DATECAN vs. ExteNET

DATECAN definition of iDFS	ExteNET trial	
	Included?	Supporting text
Death		
From breast cancer	×	
From non-breast cancer cause	×	
Related to protocol treatment	×	
From any cause	✓	Death from any cause
From unknown cause	×	

DATECAN definition of iDFS	ExteNET trial	
	Included?	Supporting text
Clinical event		
Invasive ipsilateral breast tumour recurrence/progression	(✓)	Invasive ipsilateral breast tumour recurrence
Local invasive recurrence/progression	(✓)	Local/regional invasive recurrence
Regional invasive recurrence/progression (M^+: regional progression)	(✓)	
Invasive contralateral breast cancer	✓	Invasive contralateral breast cancer
Appearance/occurrence of metastases/distant recurrence	(✓)	Distant recurrence
Second primary invasive cancer (non-breast cancer)	×	

Based on Table 2 of Gourgou-Bourgade 2015[17, 18] and Table 5 of the CS[1]
CS = company submission; DATECAN = Definition for the Assessment of Time-to-event Endpoints in CANcer trials; iDFS = invasive disease-free survival; M = metastasis; NA = not applicable

3.4 Other relevant factors

The company notes that both the ExteNET and CONTROL clinical trials are ongoing. Recently published and unpublished data are included; however, these would not have been identified by a systematic review.

The description of the decision problem within the CS does not highlight any equity or equality issues.

Neratinib is not considered by the company to meet NICE end of life criteria. [redacted]

4 Clinical effectiveness

4.1 Critique of the methods of the review(s)

4.1.1 Searches

A single set of searches were undertaken to identify clinical effectiveness and adverse events data. The company submission and response to clarification provided sufficient details for the ERG to appraise the original literature searches and both sets of 2018 update searches. A good range of databases, conference proceedings and additional resources were searched.

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[19] The submission was checked against the single technology appraisal (STA) template for company/sponsor submission of evidence.[20] The ERG has presented only the major limitations of the search strategies in the main report. Further minor comments can be found in Appendix 1.

Appendix D.1 of the CS states that MEDLINE and MEDLINE in Process (PubMed), Embase (Elsevier platform), Biosis (Dialog platform) and the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE; via the Cochrane Library) were searched to identify randomised clinical trials of neratinib and its comparator treatments in an extended adjuvant, adjuvant, or neoadjuvant therapy setting for early-stage HER2+ breast cancer. All search strategies were reported in detail in Appendix D.1. The original searches were conducted on 9 November 2016, with update searches taking place on 19-20 February 2018 and 21 November 2018. Results were limited to clinical trials. The CS states that the electronic database searches had no language limits; but in agreement with Puma, non-English language articles were excluded during the screening process. Databases were reported to have been searched from inception, although specific start dates were not provided.

Searches were conducted and reported for conference proceedings from 2016-2018 for the following conferences: International Society for Pharmacoeconomics and Outcomes Research, American Society of Clinical Oncology, European Society for Medical Oncology, European Breast Cancer Conference, San Antonio Breast Cancer Symposium.

To identify ongoing, discontinued, or completed clinical trials, the following resources were searched: ClinicalTrials.gov, International Clinical Trials Registry Platform Search Portal; Clinical Trials Register, PharmNet.Bund.

Reference lists of relevant studies, recent systematic reviews, and meta-analyses were searched to identify further relevant studies. In addition, the reference lists of relevant articles identified from the following health technology assessment (HTA) websites were also searched: NICE, Scottish Medicines Consortium, Canadian Agency for Drugs and Technologies in Health, International Network of Agencies for Health Technology Assessment, Haute Autorité de Santé, and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).

ERG comment: The selection of databases searched was adequate, and searches were clearly reported and reproducible. The database name, host and date searched were provided. An extensive range of resources additional to database searches was included in the systematic literature

review (SLR) to identify further relevant studies and grey literature. Details of the search strategies used for these resources were well documented in the CS and response to clarification.

Study design filters to identify clinical trials were applied. The filters were not referenced, so it was unclear whether they were published objectively-derived filters. The filters contained a combination of subject heading terms (MeSH and Emtree) and free text terms, and the ERG deemed them to be adequate.

The trials filter used on the Cochrane Library was unnecessary for the search of CENTRAL, which contains only controlled trials. For the searches of CDSR and DARE, a trials filter could potentially remove all records, as these databases contain only systematic reviews. The use of a trials filter for these databases therefore risks removing potentially relevant records, and negates any benefit of searching databases of systematic reviews. However, given the range of additional resources used in the SLR, it is unlikely that any relevant studies have been missed.

Separate adverse events (AE) searches were not performed, as the clinical effectiveness searches reported in section B.2 and Appendix D were also used to identify studies reporting safety data.[1, 21] The clinical effectiveness searches incorporated a methodological filter intended to limit the search to clinical trials. Guidance by the Centre for Reviews and Dissemination (CRD)[22] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. The ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits used. However, given the range of additional resources used in the SLR, it is unlikely that any relevant studies have been missed.

4.1.2 Inclusion criteria

The CS provided a table describing the inclusion and exclusion criteria based on the agreed upon strategy in order to ensure screening decisions were consistent. The CS mentioned that the presented systematic review is an update in order to identify studies relevant to the updated NICE decision problem. The component of the inclusion criteria focusing on population emphasised the focus of the submission as patients with HER2+ breast cancer rather than HER2- breast cancer (Table 4.1). After applying the listed criteria, one RCT, the ExteNET study, was found to be appropriate for inclusion in the current systematic review. The CS also presented the CONTROL study, which was used to investigate the use of neratinib with early HR+/HER2+ breast cancer. The CONTROL study was not originally found in the searches because it is not an RCT. However, the company determined the CONTROL study was relevant to the NICE decision problem and was therefore included.

Table 4.1: Detailed inclusion/exclusion criteria for the systematic literature review

Criteria	Inclusion	Exclusion
Population	• Adults aged ≥ 18 years • Patients with early stage HER2+ breast cancer without metastases (including neoadjuvant, adjuvant, or extended adjuvant treatment settings)	• Patients < 18 years • Patients with primarily other types of cancer or disease (including HER2− breast cancer and advanced or metastatic HER2+ breast cancer or other cancers)
Interventions and comparators	• Neratinib (NERLYNX®) • Trastuzumab emtansine (Kadcyla) • Trastuzumab (Herceptin) • Trastuzumab + pertuzumab (Herceptin	• Studies that did not have a comparator of interest (identified at the left) in at least 1 arm • Studies of nonpharmacological

Criteria	Inclusion	Exclusion
	+ Perjeta) • Lapatinib (Tykerb/Tyverb) • Trastuzumab + lapatinib (Herceptin + Tykerb/Tyverb)	interventions (e.g., exercise, Chinese medicine)

Outcomes[a]	• Key efficacy endpoints:
	  • DFS
	  • DDFS
	  • TTDR
	  • IDFS
	  • CNS recurrence
	  • PFS
	  • OS
	  • DFS-DCIS
	  • EFS
	  • pCR
	• Key health-related quality-of-life endpoints (e.g. EORTC, EQ-5D)
	• Adverse events
		• Studies that did not report any of the outcomes listed at the left

Study design	• Randomised, controlled, prospective clinical trials • Randomised clinical trials that compared interventions in clinical settings (e.g., pragmatic studies or phase 4 studies) • Long-term follow-up studies (e.g., open-label follow-up studies with continuation of treatments in their respective randomised group) • Systematic reviews and meta-analyses	• Comments • Letters • Editorials • Conference abstracts published prior to 2016 • Non-English language articles[b]

Based on Table 14 of CS Appendix D[21]

[a] Outcomes were only reviewed during the level 2 screening process; [b] According to section D1.1.3 of the CS appendices, *"electronic database searches had no language limits; but in agreement with Puma, non–English-language articles were excluded during the screening process"*.[21]

CNS = central nervous system; DDFS = distant disease-free survival; DFS = disease-free survival; DFS-DCIS = disease-free survival including ductal carcinoma in situ; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; HER2– = human epidermal growth factor receptor 2 negative; HER2+ = human epidermal growth factor receptor 2 positive; iDFS = invasive disease-free survival; OS = overall survival; pCR = pathologic complete response; PFS = progression-free survival; TTDR = time to distant recurrence.

ERG comment: The exclusion of non-English language articles might have missed potentially relevant articles. The ERG has no further comment on the inclusion and exclusion criteria.

4.1.3 Critique of data extraction

According to the provided appendices of the CS, data extraction was completed for each clinical trial of the comparators of interest from full-text publications. The data extraction was completed by one researcher. A quality check of the extracted data was completed by a second researcher.

ERG comment: According to the Cochrane Handbook for Systematic Reviews (section 7.6.2), *"it is strongly recommended that more than one person extract data from every report to minimize errors and reduce potential biases being introduced by review authors"*.[23] In contrast, only one person extracted relevant data (with a second person checking) for the systematic review reported in the CS, i.e. there is increased risk of errors and bias.

4.1.4 Quality assessment

The quality of the ExteNET study was assessed by the company and presented in appendices of the CS.[21] The elements that were considered in the quality assessment were appropriate randomisation, adequate concealed treatment allocation, the presence of unexpected imbalances in drop-outs between groups, any evidence suggesting the authors measured more outcomes than they reported, the inclusion of an appropriate intention-to-treat analysis, and the use of appropriate methods to account for missing data. Table 4.2 provides an overview of the quality assessment of the ExteNET study.

The quality of the CONTROL study was also assessed by the company and presented in appendices of the CS.[21] Table 4.3 provides an overview of the quality assessment of the CONTROL study.

Table 4.2: Quality assessment of ExteNET (NCT00878709)

Study question	How is the question addressed in the study? (as reported in the CS)	Grade (Yes/No/Not Clear/NA)	ERG comment
Was randomisation carried out appropriately?	Patients were randomly assigned (1:1) to receive neratinib or matching placebo. The randomisation sequence was generated with permuted blocks stratified by locally determined hormone receptor status, nodal status, and trastuzumab adjuvant regimen.	Yes	Agreement
Was the concealment of treatment allocation adequate?	The randomisation was performed via an interactive voice and web-response system.	Yes	Agreement
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline characteristics were well balanced across treatment groups and between the ITT and label population	Yes	Agreement
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators, and trial sponsors were masked to treatment allocation.	Yes	Agreement
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The patient flow diagram was provided and all the reason for discontinuations were accounted for. There was a difference in attrition rate between the 2 groups, mainly because of early adverse events in the neratinib group. A sensitivity analysis assessing the effect of early drop-outs on invasive disease-free survival yielded results that were consistent with those of the primary analysis. Baseline characteristics were similar in patients who dropped out before 3 months and in those who continued beyond 3 months for both treatment groups.	Yes	Agreement

Study question	How is the question addressed in the study? (as reported in the CS)	Grade (Yes/No/Not Clear/NA)	ERG comment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All measurements listed in methods were reported.	No	OS not reported. DFS defined by CS
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analysis of the primary endpoint, invasive disease-free survival (where invasive disease was defined as invasive ipsilateral tumour recurrence, invasive contralateral breast cancer, local or regional invasive recurrence, distant recurrence, or death from any cause), was performed on the ITT population, defined as all randomly assigned patients. Furthermore, all secondary endpoints were analysed using the ITT approach: disease-free survival, including ductal carcinoma in situ, time to distant recurrence, distant disease-free survival, overall survival, and safety. The methods of accounting for missing data were not reported.	Yes	Agreement Adverse events were reported for the safety population defined as all patients who received at least one dose of study treatment. Patients were analysed according to the treatment they received.
Did the authors of the study publication declare any conflicts of interest?	ExteNET was funded by Wyeth, Pfizer and Puma. Six authors were employees of Puma Biotechnology; three authors received grants from Puma during the conduct of the study.	Yes	Agreement
Does the trial reflect routine clinical practice in England?	ExteNET included 80 patients at 13 sites in the UK where neratinib was used in a research setting within UK NHS hospitals; therefore, results should be generalisable to UK clinical practice.	Yes	Disagreement (see ERG comment below)

Based on Table 27 of the CS appendices[21]

CS = company submission; DFS = disease-free survival; ERG = Evidence Review Group; ITT = intention-to-treat; OS = overall survival; UK = United Kingdom

Table 4.3: CASP quality assessment of CONTROL (NCT02400476)

Study question	Grade (yes/no/unclear)	ERG comment
1. Did the study address a clearly focused issue?	Yes The CONTROL study was designed to investigate the efficacy of anti-diarrheal prophylaxis in patients ≥ 18 years with early HER2+ breast cancer receiving neratinib and who had previously completed trastuzumab (neo)adjuvant therapy.	Agreement
2. Did the authors use an appropriate method to answer their question?	No An RCT would be the most appropriate method in order to reduce potential bias.	Agreement
3. Was the cohort recruited in an acceptable way?	Unclear Details on recruitment are not reported.	Agreement
4. Was the exposure accurately measured to minimise bias?	Yes Patients in all cohorts receive neratinib 240 mg/day for 1 year (13 cycles). Patients in the loperamide cohort received either i) 4 mg initial dose, then 2 mg Q4h d1-3, then 2 mg Q6-8h d4-56 (original protocol) or ii) 4 mg initial dose, then 4 mg TID d1-14, then 4 mg BID d15-56. Patients in the budesonide cohort received budesonide 9 mg QD for one cycle and loperamide 4 mg initial dose, then 4 mg TID d1-14, then 4 mg BID d15-56. Patients in the in the colestipol cohort received colestipol 2 g BID for 1 cycle and loperamide 4 mg initial dose, then 4 mg TID d1-14, then 4 mg BID d15-28.	Agreement
5. Was the outcome accurately measured to minimise bias?	Yes The primary endpoint of grade ≥ 3 diarrhoea and the secondary endpoints of frequency distribution of maximum-grade diarrhoea, incidence and severity of diarrhoea by loperamide exposure, SAEs, and AEs of interest were graded according to NCI-CTCAE (version 4.0). The exploratory endpoint of patient-reported HRQoL was assessed using FACT-B version 4.0 and EQ-5D-5L. Additionally, exploratory biomarker analysis for disease recurrence were analysed.	Agreement
6A. Have the authors identified all important confounding factors?	Yes The possibility of conducting an RCT is not discussed. The authors consider the small samples size to be a confounding factor in the HRQoL analysis	Agreement

Study question	Grade (yes/no/unclear)	ERG comment
6B. Have they taken account of the confounding factors in the design and/or analysis?	Yes The small samples size as a confounding factor in the HRQoL analysis is discussed.	Agreement
7A. Was the follow-up of subjects complete enough?	Yes/Unclear The study is ongoing. The final analysis will be performed when all patients have completed the planned 12 months of neratinib therapy. In October 2018, 100% of the loperamide- and loperamide-budesonide cohorts and 95% of the colestipol-loperamide cohort have completed the study treatment.	Agreement
7B. Was the follow-up of subjects long enough?	Yes/Unclear The study is ongoing. The final analysis will be performed when all patients have completed the planned 12 months of neratinib therapy. In October 2018, 100% of the loperamide- and loperamide-budesonide cohorts and 95% of the colestipol-loperamide cohort have completed the study treatment.	Agreement
8. What are the results of this study?	A structured loperamide prophylactic regimen for one or two cycles with or without the addition of either budesonide or colestipol for a single cycle, reduces the incidence, severity, and duration of neratinib-associated diarrhoea compared with that observed in the ExteNET trial. Incidence of grade ≥ 3 diarrhoea was as follows: loperamide 30.7% (95% CI, 23.1-39.1); loperamide with budesonide 26.6% (95% CI, 16.3-39.1); loperamide with colestipol 10.8% (95% CI, 5.9-17.8); ExteNET historical control 39.9% (95% CI, 37.3-42.5). Any HRQoL impairment is short-lived and does not reach predefined clinically meaningful thresholds in the loperamide cohort. However, the small sample size and lack of within-study comparator arm limits the conclusions that can be drawn from these data.	Agreement
9. How precise are the results?	95% confidence intervals are used throughout.	The reported confidence intervals are relatively wide, reflecting the small study size
10. Do you believe the results?	Yes The results are believable. An RCT would be the most appropriate method to reduce potential bias; however, outcomes were graded and reported using validated scales and criteria.	Agreement

Study question	Grade (yes/no/unclear)	ERG comment
11. Can the results be applied to the local population?	Yes The results are generalisable to the local population. CONTROL did not include any European sites; however, the anti-diarrhoeal prophylaxis regimens used in the study (such as loperamide) are commonly used in UK clinical practice to treat chemotherapy-induced diarrhoea, so results are generalisable to the UK NHS (see Appendix M of the CS for further details).[21]	The ERG has some concerns regarding the applicability of these findings to the UK context (please see ERG comment below)
12. Do the results of this study fit with other available evidence?	Unclear There are no other studies reporting the incidence of neratinib-associated diarrhoea apart from ExteNET. Other than diarrhoea, the tolerability profile of neratinib with diarrhoea prophylaxis was generally similar to that reported in ExteNET, with similar rates of AEs. Grade 1/2 constipation was more common in CONTROL than in ExteNET, but few patients (loperamide, n = 3; colestipol, n = 2) discontinued treatment as a result. Two grade 4 AEs were reported in CONTROL, but both were considered unrelated to treatment.	Apart from ExteNET, the ERG is not aware of any other study reporting the incidence of neratinib-associated diarrhoea
Did the authors of the study publication declare any conflicts of interest?	Unclear Publications did not report any conflicts of interest; however, the study was funded by Puma Biotechnology and some study authors are employees of Puma.	Agreement
Does the trial reflect routine clinical practice in England?	Unclear CONTROL did not include any UK sites, however the anti-diarrhoeal prophylaxis treatments used in CONTROL, such as loperamide, are standardly used alongside chemotherapy regimens in the UK.	The ERG has some concerns regarding the applicability of these findings to the UK context (please see ERG comment below)

Based on Table 28 of the CS appendices[21]

AE = adverse event; bid = twice daily; CASP = Critical Appraisal Skills Programme; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D-5L = EQ-5D 5-level; ERG = Evidence Review Group; FACT-B = Functional Assessment of Cancer Therapy-Breast; HER2+ = human epidermal growth factor receptor 2-positive; HRQoL = health-related quality of life; mg = milligram; NHS = National Health Service; NCI = National Cancer Institute; q4h = once every four hours; RCT = randomised controlled trial; SAE = serious adverse event; tid = three times a day; UK = United Kingdom

ERG comment: The ERG has concerns regarding two issues in the quality assessment of ExteNET:

1. As detailed in section 3.3 of the ERG report, regarding OS, [redacted]. Furthermore, the definition of DFS is based on iDFS for which a definition narrower than the standard definition was used (see section 3.3 for details).
2. There are concerns regarding the representativeness of the neratinib trial to the UK population. As stated by the company in their clarification response to question A11 (regarding further results on the label population of ExteNET), "*the number of UK patients is too small to perform an appropriate statistical test"*, which causes some concern to the ERG.[16] ExteNET included *"80 patients at 13 sites in the UK"*, however, .only 41 (19 in the neratinib arm and 22 in the placebo arm) of these were in the label population.[1, 16]

Furthermore, the ERG has a number of concerns regarding the CONTROL study:

1. CONTROL has been described as an *"international, sequential-cohort, open-label, phase II study"*.[24] As indicated in the quality assessment by the company, *"an RCT would be the most appropriate method in order to reduce potential bias"*.[21]
2. As stated in the quality assessment by the company, *"details on recruitment are not reported"*.[21] Given that Puma Biotechnology is the funder of the trial, this statement is surprising.
3. The CS acknowledges the small sample size of the study. The uncertainty in the results due to the small sample size is reflected by the relatively wide confidence intervals.
4. The study is ongoing and the *"final analysis will be performed when all patients have completed the planned 12 months of neratinib therapy. In October 2018, 100% of the loperamide- and loperamide-budesonide cohorts and 95% of the colestipol-loperamide cohort have completed the study treatment"*.[21]
5. As noted by the company, *"CONTROL did not include any European sites"*.[21] While the ERG agrees that *"the antidiarrhoeal prophylaxis regimens used in the study (such as loperamide) are commonly used in UK clinical practice to treat chemotherapy-induced diarrhoea"*, it has some concerns regarding the applicability to the UK setting as participants recruited for the trial as well as the health care settings in which participants were studied in could be different.

4.1.5 Evidence synthesis

Only one RCT, ExteNET, was identified. Therefore, no evidence synthesis was done.

4.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

A key concern by the ERG is the surrogate outcome measure used by the company as the primary endpoint of the ExteNET trial. As detailed in section 3.3, the definition the company used for iDFS was narrower than the standard definition (Table 3.2).[17] Given the narrower definition, iDFS events might have been missed in both arms of the ExteNET trial. Furthermore, as the ExteNET study did not measure DFS, it is impossible to validate this measure and to justify its use, i.e. the ERG cannot be sure that all aspects of DFS were fully captured by this surrogate outcome, which raises serious concerns.

Other technology appraisals that have used iDFS as a primary measure, have also measured DFS on its own to demonstrate the validity of the measure. Table 4.4 shows the summary of selected primary and secondary endpoints for the ITT population technology appraisal (TA569: Pertuzumab for adjuvant treatment of HER2-positive early breast cancer).[25] Although, both measures of iDFS seem relatively similar to DFS, there is a significant difference between iDFS (both measures) and OS which highlights some uncertainty as to whether iDFS is an appropriate surrogate measure of OS.

In the CS, iDFS is used as a surrogate for OS in this appraisal as the company claims that the OS data are not yet mature and [redacted]. The ERG is concerned about the use of DFS as a surrogate outcome for OS in breast cancer trials as benefits in DFS may not translate to benefits in OS. However, a systematic review published in 2019 included eight trials evaluating adjuvant treatment for HER-2 positive early breast cancer and analysed the association between DFS and OS using both patient- and trial-level data.[26] It found a strong association between DFS and OS with a treatment level association ≥ 0.75 suggesting that DFS may have good statistical validity to be used as a surrogate for OS in HER-2 positive early breast cancer, particularly following 12 months of treatment with trastuzumab. Overall, the ERG is uncertain to the extent to which iDFS translates into long-term OS benefits and whether iDFS is an acceptable surrogate for DFS as well as whether DFS is an acceptable surrogate outcome for OS in the label population.

Table 4.4: Comparison of DFS and iDFS and OS from pertuzumab appraisal

Endpoint	Hazard ratio (95% CI)	Pertuzumab + trastuzumab + chemotherapy n=2,400	Placebo + trastuzumab + chemotherapy n=2,404c	p-value
iDFS primary efficacy parameter, an estimated 3-year event-free rate, %	0.81 (0.66 to 1.00)	94.1	93.2	0.045
iDFS including second no primary breast cancer events (STEEP definition)[27]	0.82 (0.68 to 0.99)	93.5	92.5	0.043
DFS	0.81 (0.67 to 0.98)	93.4	92.3	0.033
OS	0.89 (0.66 to 1.21)	97.7	97.7	0.467

Based on Table 12 of TA569[25]
CI = confidence interval; DFS = disease-free survival; iDFS = invasive disease-free survival; OS = overall survival; TA = technology appraisal

4.2.1 Overview of the direct evidence in the submission

The company submitted evidence from two key trials. The main trial was a phase III randomised control trial (RCT), ExteNET, which compared neratinib to placebo in adults with early HR+, HER2+ breast cancer who are within one year of finishing trastuzumab therapy (Table 4.5).[1]

Table 4.5: Clinical effectiveness evidence for neratinib – ExteNET trial methodology summary

Trial name	ExteNET trial
Population	Women with early-stage HER2-overexpressed/amplified breast cancer following trastuzumab in the adjuvant setting who are receiving neratinib versus placebo.
Intervention	Neratinib (n=1,420)

Trial name	ExteNET trial
Comparator	Placebo (n=1,420)
Outcomes	**Primary** - Invasive disease-free survival **Secondary** - Disease free survival – ductal carcinoma in situ - Time to distant recurrence - Distant disease-free survival - Cumulative incidence of central nervous system recurrence - Overall survival - Safety
Study design	ExteNET is an ongoing, randomised, double-blind, placebo-controlled, multi-centre, international, phase III study.
Duration of trial and trial phases	Neratinib given for 12 months, unless disease recurrence or new breast cancer, intolerable adverse even, or consent withdrawal occurred
	Dose reductions (200 mg, 160 mg, 120 mg per day) were allowed for toxicity, with treatment stopped if the lowest does was not tolerated or if treatment was interrupted for more than 3 weeks.
Settings and locations where the data were collected	495 sites in 40 countries in Europe, Asia, New Zealand, North America, and South America (13 sites in the UK)[1]
Based on Table 4 and Figure 5 of the CS[1] [1] A full breakdown by country cannot be provided by the ERG as the relevant section of the CSR (Table 58, section 14.1.1.2 Summary of Enrolment by Country and Site, All Enrolled Patients) was not provided by the company, despite a request by the ERG to provide the full CSR. CS = company submission; CSR = clinical study report: ERG = Evidence Review Group: HER2 = Human epidermal growth factor receptor 2; mg = milligram; UK = United Kingdom	

CONTROL is an ongoing, phase 2, open-label safety and tolerability study investigating the effect of structured anti-diarrhoeal strategies (such as loperamide prophylaxis with or without budesonide or colestipol) on the incidence of neratinib-associated diarrhoea, the most common side effect observed in the ExteNET trial (Table 4.6).[1]

Table 4.6: Clinical effectiveness evidence for neratinib – CONTROL trial methodology summary

Trial name	ExteNET trial
Population	Women with early-stage HER2-overexpressed/amplified breast cancer following trastuzumab in the adjuvant setting who are receiving neratinib versus placebo.
Intervention	Neratinib + loperamide (n=137, loperamide cohort) Neratinib + loperamide + budesonide (n=64, budesonide cohort) Neratinib + loperamide + colestipol (n=120, colestipol cohort) Neratinib + colestipol + loperamide as needed (recruitment ongoing) Neratinib dose escalation during cycle 1 + loperamide as needed (recruitment ongoing) Neratinib dose escalation during cycle 2 + loperamide given as needed (recruitment ongoing)

Trial name	ExteNET trial
Comparator	Neratinib – only cohort form ExteNET (n=1,420)
Outcomes	Primary: Incidence of grade ≥ 3 diarrhoea during treatment with neratinib Secondary: Anti-diarrhoeal treatment exposure and incidence and severity of diarrhoea (such as loperamide with or without budesonide or colestipol) Assessment of the incidence of serious AEs and other AEs of special interest
Study design	CONTROL is an ongoing open label, phase II, safety and tolerability study
Settings and locations where the data were collected	52 sites in USA, Canada, Australia and Spain

Based on Table 9 of the CS[1]
CS = company submission; HER2 = human epidermal growth factor receptor 2; mg = milligram; UK = United Kingdom; USA = United States of America

ERG comment: The main concern of the ERG regarding ExteNET is the lack of availability of OS data and the use of a surrogate outcome measure for DFS, iDFS. The company's primary iDFS endpoint was defined as *"time from randomisation to the first recurrence of the following DFS events: invasive ipsilateral breast cancer recurrence, local/regional invasive recurrence, distant recurrence, death from any cause or invasive contralateral breast cancer"* (see section 3.3 and beginning of section 4.2 for details).[1]

ExteNET included *"80 patients at 13 sites in the UK"*, however, only 41 (19 in the neratinib arm and 22 in the placebo arm) of these were in the label population.[1, 16] In regards to the CONTROL study, having no centres in the UK and only one centre in Spain (which is currently recruiting), and no others in Europe poses a question of the generalisability to the UK population.

4.2.2 Participants in the included studies

4.2.2.1 Participants in the ExteNET trial

In the ExteNET study, in order to be included patients had to be adults who had histologically confirmed primary adenocarcinoma of the breast that was HER2+ by one of three protocol defined assays. The patients also had to test negative in clinical and radiologic assessments for local or regional recurrence disease or metastatic disease at the time of study entry. The ER/PR status of all patients had to be known at the entry of the study. Further inclusion criteria also included adequately treated primary breast cancer with surgery, as defined by prior mastectomy or lumpectomy, with margins clear of invasive carcinoma and DCIS. In order to be included in ExteNET study patients must have completed a course of trastuzumab in the adjuvant setting previously within the last year. Two thousand eight hundred and forty patients were included in the ITT population, of which 1,334 were of the label population (HR+ completing prior trastuzumab ≤ 1 year from randomisation), with n=670 in the neratinib arm and n=664 in the placebo arm. Randomisation was stratified by three factors: HR+ (ER+ and/or PR+) versus HR– (ER– and PR–); nodal status (0, 1-3 vs. 4 or more positive nodes) and prior trastuzumab given sequentially versus concurrently with chemotherapy. Table 4.7 indicates the demographics of the patients included in the ExteNET study.

The label population is the one that is of interest to the ERG and in the scope of this appraisal so only that shall be discussed. It should be noted that power calculations were conducted for the ITT population but not the label population. The mean age of the participants in the ExteNET study in both the neratinib and placebo was 51 years. And all other characteristics seem to be well matched in both arms of the study.

Table 4.7: Patient demographics, baseline disease characteristics, and prior anti-cancer therapies for the ITT and label population of the ExteNET study

Characteristic	ITT		Label population	
	Neratinib (n=1,420)	Placebo (n=1,420)	Neratinib (n=670)	Placebo (n=664)
Demographic				
Age, years (median [range])	52 (25-83)	52 (23-82)	51 (25-83)	51 (23-78)
Region				
North America	519 (37%)	477 (34%)	237 (35.4)	205 (30.9)
Western Europe, Australia, and South Africa	487 (34%)	532 (38%)	236 (35.2)	264 (39.8)
Asia Pacific, Eastern Europe, and South America	414 (29%)	411 (29%)	197 (29.4)	195 (29.4)
Menopausal status at diagnosis				
Premenopausal	663 (47%)	664 (47%)	350 (52.2)	342 (51.5)
Postmenopausal	757 (53%)	756 (53%)	320 (47.8)	322 (48.5)
Nodal status [a]				
Negative	335 (24%)	336 (24%)	130 (19.4)	125 (18.8)
1-3 positive nodes	664 (47%)	664 (47%)	339 (50.6)	334 (50.3)
≥ 4 positive nodes	421 (30%)	420 (30%)	201 (30.0)	205 (30.9)
HR status				
Positive (ER+, PR+, or both)	816 (58%)	815 (57%)		
Negative (ER– and PR–)	604 (43%)	605 (43%)		
Previous trastuzumab regimen				
Given concurrently with chemotherapy	884 (62%)	886 (62%)	411 (61.3)	415 (62.5)
Given sequentially with chemotherapy	536 (38%)	534 (38%)	259 (38.7)	249 (37.5)
T stage				
T1	440 (31%)	459 (32%)	218 (32.5)	209 (31.5)
T2	585 (41%)	555 (39%)	270 (40.3)	250 (37.7)
≥ T3	144 (10%)	117 (8%)	61 (9.1)	65 (9.8)
Unknown	250 (18%)	288 (20%)	121 (18.1)	140 (21.1)
Missing	1 (< 1%)	1 (< 1%)	0	0
Prior neoadjuvant or adjuvant therapy [b]				
Trastuzumab	1,420 (100%)	1,420 (100%)	670 (100.0)	664 (100.0)
Anthracycline only	136 (10%)	135 (10%)	67 (10.0)	58 (8.7)

Characteristic	ITT		Label population	
	Neratinib (n=1,420)	Placebo (n=1,420)	Neratinib (n=670)	Placebo (n=664)
Anthracycline plus taxane	962 (68%)	965 (68%)	435 (64.9)	445 (67.0)
Taxane only	318 (22%)	316 (22%)	167 (24.9)	159 (23.9)
Neither anthracycline or taxane	4 (< 1%)	4 (< 1%)	1 (0.1)	2 (0.3)
Duration of prior adjuvant trastuzumab therapy, months (median [range])	11.5 (10.9-11.9)	11.4 (10.8-11.9)	11.4 (1.4-29.1)	11.4 (1.4-24.0)
Time from last dose of trastuzumab to randomisation, months (median [IQR])	4.4 (1.6-10.4)	4.6 (1.5-10.8)	3.07 (0.2-12.0)	3.30 (0.3-12.0)
Prior endocrine therapy use for HR+ tumours,[c] n (%)				
No	56 (7%)	51 (6%)	38 (5.7)	30 (4.5)
Yes	760 (93%)	764 (94%)	632 (94.3)	634 (95.5)
Antioestrogen only	375 (46%)	347 (43%)	340 (50.7)	317 (47.7)
Antioestrogen and aromatase inhibitor (sequential)	20 (3%)	34 (4%)	29 (4.3)	24 (3.6)
Aromatase inhibitor only	362 (44%)	379 (47%)	259 (38.7)	290 (43.7)
Non–antioestrogen or aromatase inhibitor	3 (< 1%)	4 (< 1%)	4 (0.6)	3 (0.5)

Based on Tables 7 and 8 of the CS[1]

[a] The number of positive nodes was at the time of initial diagnosis (for patients who received adjuvant therapy) or surgery (for those who received neoadjuvant therapy). Patients with residual invasive disease in the breast, but node-negative disease or unknown nodal status in the axilla, after neoadjuvant therapy were included under 1-3 positive nodes; [b] The proportion of patients who received neoadjuvant chemotherapy was 25% (n=247) in the neratinib group and 27% (n=282) in the placebo group; [c] Percentage is based on the number of patients with HR+ tumours. Tumours were assessed as being ER+ and PR+ on the basis of local pathology laboratory cut-offs. There was no protocol specification as to whether a 1% or 10% threshold should be used

CS = company submission; ER- = oestrogen receptor-negative; ER+ = oestrogen receptor-positive; HR = hormone receptor; IQR = interquartile range; ITT = intention-to-treat; PR- = progesterone receptor-negative; PR+ = progesterone receptor-positive

4.2.2.2 Participants in the CONTROL trial

In the CONTROL study, included patients had to be adults who had histologically confirmed stage I-IIIC primary adenocarcinoma of the breast.[1] Patients also had to be documented HER2 overexpression or gene amplified tumour by a validated method and must have completed a prior course of adjuvant trastuzumab therapy, with the last dose of trastuzumab given > 2 weeks and < 2 years (365 days) from enrolment. At the time of entry, clinical and radiologic assessments had to be negative for local or regional recurrence of disease or metastatic disease. The 3rd November 2017 was the cut-off date for the interim safety analyses. At this point, the population comprised of 321 patients all of whom had received at least one dose of neratinib.

The safety population consisted of three cohorts: loperamide cohort (n=137), budesonide cohort (n=64; still actively recruiting), and colestipol cohort (n=120). According to the CS, baseline characteristics were similar in CONTROL and ExteNET; however, the following differences were noted:

- more CONTROL patients had HR+ tumours,

- more had received taxanes,
- fewer had received anthracyclines, but
- more ExteNET patients had stage III tumours at diagnosis.

Additionally, 40% to 63% of patients in CONTROL, but none in ExteNET, had received pertuzumab as either neoadjuvant or adjuvant therapy.

The population of the CONTROL study includes all patients with early HER2+ breast cancer, regardless of HR status. However, the indication of the drug is narrower; patients with HR+/HER2+ breast cancer who have completed a course of adjuvant trastuzumab less than one year ago. The company submission states show that most of the safety population of CONTROL had HR+/HER2+ breast cancer (72%-75%) and the median time since last trastuzumab dose in all cohorts was less than 4.3 months. Table 4.8 presents an overview of the baseline characteristics of the CONTROL study.

Table 4.8: Baseline disease characteristics for the interim analysis population of CONTROL

	CONTROL			ExteNET
Characteristic	**Loperamide cohort**	**Budesonide + loperamide cohort**	**Colestipol + loperamide cohort**	**Neratinib arm (loperamide as needed)**
N (at data cut-off[a])	137	64	120	1,420
Median age (range), years	53 (30-86)	49 (29-78)	53 (26-78)	52 (25-83)
Tumour stage at diagnosis, %				
I	28.5	25.0	16.7	9.8
IIA, IIB	54.7	46.9	46.7	42.0
IIIA, IIIB, IIIC	14.6	23.4	26.7	31.2
IV	0.7	0	0.8	0
Hormone receptor status, %				
Positive (ER+ and/or PR+)	75.2	71.9	72.5	57.5
Negative (ER– and PR–)	24.8	28.1	26.7	42.5
Prior (neo)adjuvant therapy, %				
Trastuzumab	99.3	96.9	99.2	100
Taxanes	95.6	96.9	98.3	77.3
Anthracycline	26.3	28.1	24.2	90.1
Pertuzumab	40.1	60.9	62.5	–
Median (range) duration of prior trastuzumab, months[b]	11.5 (2.4-18.2)	10.9 (9.8-11.6)	11.0 (10.0-11.8)	11.5 (0.7-56.9)
Median (range) time since last trastuzumab dose, months	3.9 (0.1-12.1)	4.3 (0.5-17.1)	2.7 (0.0-18.6)	4.4 (0.2-30.9)

Based on Table 10 of the CS[1]

[a] Data cut-off: 3 November 2017; [b] Patients with a median time since last trastuzumab dose > 12 months are considered protocol deviations for the entry criteria and will be removed from the final analysis.

CS = company submission; ER = oestrogen receptor-negative; ER+ = oestrogen receptor-positive; PR- =

	CONTROL			ExteNET
Characteristic	**Loperamide cohort**	**Budesonide + loperamide cohort**	**Colestipol + loperamide cohort**	**Neratinib arm (loperamide as needed)**
Progesterone receptor-negative; PR+ = Progesterone receptor-positive				

ERG comment: In the ExteNET study, the participants seem to be well matched in the placebo and treatment arm. However, the ERG had some concerns over the stratification by nodal status criterion.

The CS stated that *"patients with residual invasive disease in the breast but node-negative or unknown nodal status in the axilla after neoadjuvant therapy were included under "1-3" positive nodes"*.[1] This could possibly imply that patients with a negative nodal status be classified in the positive category, which may bias subsequent analysis. Therefore, the ERG asked for further clarification as to why the company thought this was appropriate and how many patients were of unknown status at the clarification stage. In response to question A11, the company clarified that only 2.2% of the patients had an unknown nodal status (neratinib n=14; placebo n=15).[16] As this is a relatively small percentage of the trial population, the ERG believe this would not have a relevant impact on the analysis. However, the company did not provide an explanation as to why patients with residual invasive disease in the breast but node-negative were also classified in the "1-3" positive node status, nor did the company provide the number of patients in this category. Therefore, it is unclear what impact this would have on any subsequent analysis, if any.

In the CONTROL study, the ERG noticed that nodal status of patients at baseline were not presented, therefore, it is unclear if this was assessed. Considering that the company thought nodal status was important enough to stratify by in the ExteNET trail, it is unclear why it was not observed in the CONTROL study. There is a distinct possibility that nodal status may affect the severity of the diarrhoea (primary outcome), however, as these data are not provided, the ERG cannot confirm this effect.

4.2.3 Efficacy outcomes

Key efficacy outcomes from the ExteNET trial are summarised in Table 4.9.

Figures 4.1 and 4.2 present the two-year and the five-year DFS in HR+ participants of the ITT population who had prior adjuvant trastuzumab ≤ 1 year (label population).

Table 4.9: Key efficacy outcomes for neratinib versus placebo from the ExteNET RCT (label population: HR+ population who are within one year of completion of trastuzumab)

	Neratinib (n=670)	Placebo (n=664)	Effect estimate[a]
Estimated 2-year event free rates[b]			
DFS	NR[c]	NR[c]	NR[c]
iDFS	95.3%	90.8%	HR 0.49 (95% CI 0.30 to 0.78)
DFS-DCIS	95.3%	90.0%	HR 0.45 (95% CI 0.28 to 0.71)
CNS recurrence	0.34%	1.01%	NR
TTDR	96.3%	93.3%	HR 0.53

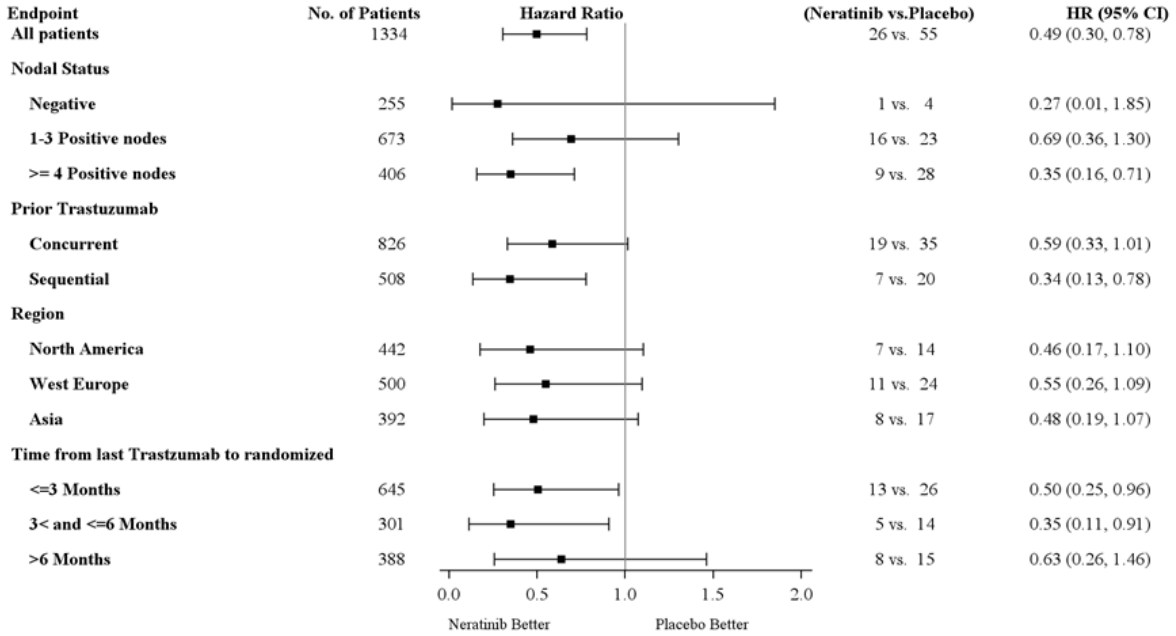
	Neratinib (n=670)	Placebo (n=664)	Effect estimate[a]
			(95% CI 0.30 to 0.89)
DDFS	96.1%	92.9%	HR 0.53 (95% CI 0.31 to 0.88)
OS	NR[d]	NR[d]	NR[d]
Estimated 5-year event free rates[b]			
DFS	NR[c]	NR[c]	NR[c]
iDFS	90.8%	85.7%	HR 0.58 (95% CI 0.41 to 0.82)
DFS-DCIS	90.6%	84.8%	HR 0.55 (95% CI 0.39 to 0.77)
CNS recurrence	0.69%	2.09%	NR
TTDR	92.6%	88.2%	HR 0.58 (95% CI 0.39 to 0.85)
DDFS	92.4%	87.7%	HR 0.57 (95% CI 0.39 to 0.83)
OS	NR[d]	NR[d]	NR[d]
Health-related quality of life (HRQoL)			
HRQoL	NR[e]	NR[e]	NR[e]

Based on Tables 15 and 16 of the CS

[a] Unstratified Cox proportional hazards model; [b] Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported; c According to the CS, *"DFS includes iDFS, DFS-DCIS, and distant DFS, which were all outcomes in ExteNET"*; [d] OS data from ExteNET [redacted]; [e] Only reported in the ITT population. Although section B.3.4.1 of the CS[1] suggests that results in the label population are available, relevant data were not available to the ERG

CI = confidence interval; CNS = central nervous system; CS = company submission; DDFS = distant disease-free survival; DFS = disease-free survival, DFS-DCIS = disease-free survival including ductal carcinoma in situ; ERG = Evidence Review Group; HR = hazard ratio; HRQoL = health-related quality of life; iDFS = invasive disease-free survival; ITT = intention-to-treat; NR = not reported; OS = overall survival; TTDR = time to distant recurrence

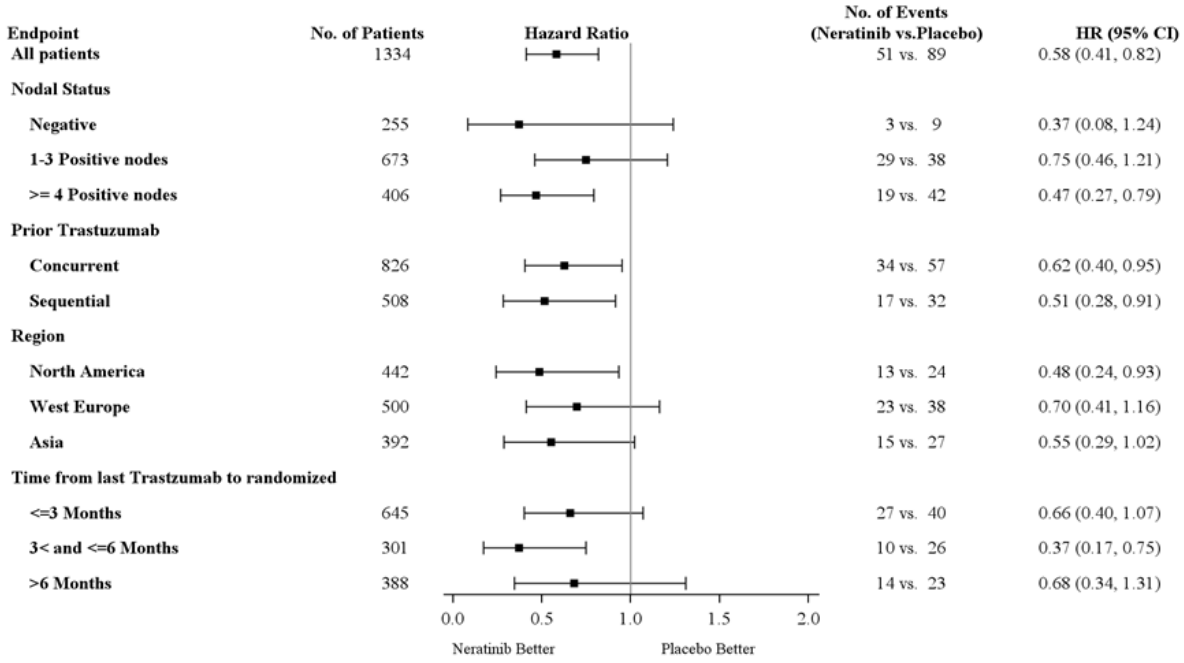
Figure 4.1: Forest plot of two-year DFS in HR+ participants of the ITT population who had prior adjuvant trastuzumab ≤ 1 year (label population)



Based on Figure 14.2.9.4.1 of the CSR, included in the response to request for clarification[16]

CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive; ITT intention-to-treat

Figure 4.2: Forest plot of five-year DFS in HR+ participants of the ITT population who had prior adjuvant trastuzumab ≤ 1 year (label population)



Based on Figure 14.2.9.4.2 of the CSR, included in the response to request for clarification[16]

CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive; ITT intention-to-treat

ERG comment: Where reported, efficacy outcomes favour neratinib over placebo. However, as discussed in section 3.3 as well as at the beginning of section 4.2, the ERG has some concerns regarding the absence of OS data as well as the narrower definition used for iDFS which has been used as a surrogate for DFS (which due to the absence of OS data is the main efficacy outcome of interest).

Figures 4.1 and 4.2 present the two-year and the five-year DFS in HR+ participants of the ITT population who had prior adjuvant trastuzumab ≤ 1 year (label population). The ERG wanted to highlight relevant differences when participants are compared by geographical region, e.g. in Figure 4.2, DFS is statistically significantly in favour of neratinib compared to placebo in North American participants (hazard ratio 0.48, 95% CI 0.24 to 0.93) but not West European participants (hazard ratio 0.70, 95% CI 0.41 to 1.16). This is consistent to other findings in these subgroups reported for other outcomes in response to request for clarification (not shown here) and underlines the concerns regarding the applicability of the trial results to a UK setting (see section 4.1.4).[16]

4.2.4 Adverse events (AEs)

AE and other safety outcomes for neratinib were identified in both CONTROL and ExteNET studies.

The safety population of CONTROL (n=321) included all patients with HER2+ breast cancer regardless of HR status or time from completion of the trastuzumab therapy, making the population wider than the scope of this appraisal. The population from CONTROL was compared with neratinib groups from the ExteNET safety population (n=1,420). The CS noted that the incidence and severity of AEs between the neratinib and placebo groups were comparable.[1]

In the ExteNET study, the most frequently reported treatment-emergent adverse events (TEAEs) with neratinib in both the safety and label population are diarrhoea, nausea, headache and abdominal pain. Discontinuation due to treatment emergent AEs were significantly different between the treatment and placebo arm in the label population, with 178 (26.9%) patients discontinuing in the neratinib arm and 30 (4.6%) in the placebo arm (Table 4.10).[1]

In ExteNET, diarrhoea is the most common TEAE in participants treated with neratinib. According to the CS grade 1-2 diarrhoea was present in 365 (55.1) in the neratinib arm and 213 (32.4) in the label population; and grade 3 was present in 261 (39.4) and seven (1.1) in neratinib and placebo groups respectively (Table 4.11). No Grade 4 TEAEs were reported in either treatment arms. The effects of diarrhoea on HRQoL in the ExteNET study were evaluated using the Functional Assessment of Cancer Therapy-Breast (FACT-B) scale, with the highest physical well-being score at 24.5, 22.9 and 21.8 with patients with grade 1, grade 2 and grade ≥ 3 diarrhoea respectively.[1]

While in the ExteNET study prophylaxis was not mandated in the protocol, the CONTROL study investigated various anti-diarrhoeal regimens, such as loperamide prophylaxis with and without budesonide or colestipol. It should be noted that [redacted][16]

The CS presented results from the CONTROL interim analysis of the safety population, i.e. regardless HR status and time from trastuzumab therapy, using a cut-off date of 3 November 2017.[1] The CS stated that the results of CONTROL study showed loperamide prophylaxis in the first cycle of neratinib treatment reduced the incidence, severity, and duration of neratinib-associated diarrhoea compared with ExteNET. The primary outcome, incidence of grade ≥ 3 diarrhoea at any time during

neratinib treatment was 30.7% (95% CI, 23.1%-39.1%) in the loperamide cohort, 26.6% (95% CI, 16.3%-39.1%) in the budesonide cohort, and 10.8% (95% CI, 5.9%-17.8%) in the colestipol cohort compared with 39.9% (95% CI, 37.3%-42.5%) in the without loperamide prophylaxis in the ExteNET trial (not mandated by protocol).[1]

Diarrhoea-related neratinib discontinuation rates decreased in each successive cohort (20% for loperamide, 11% for budesonide, and 2% for colestipol) and were less frequent with budesonide and colestipol versus ExteNET (17%) (Table 4.12). Besides diarrhoea, the overall tolerability profile of neratinib with organised anti-diarrhoeal prophylaxis (such as loperamide given with or without budesonide or colestipol) was similar to that reported in ExteNET.

Table 4.10: Overall summary of treatment emergent adverse event for neratinib in ExteNET

Safety population			
	Neratinib (n=1,408), n (%)	**Placebo (n=1,408), n (%)**	**Total (n=2,816), n (%)**
ITT population			
Any TEAE	1,387 (98.5)	1,240 (88.1)	2,627 (93.3)
Grade 3 or 4 TEAE	700 (49.7)	184 (13.1)	884 (31.4)
Fatal TEAE	2 (0.1)	1 (0.1)	3 (0.1)
Serious TEAE (SAE)	103 (7.3)	85 (6.0)	188 (6.7)
Treatment-related TEAE	1,353 (96.1)	805 (57.2)	2,158 (76.6)
Serious treatment-related TEAE	42 (3.0)	8 (0.6)	50 (1.8)
TEAE leading to treatment discontinuation	388 (27.6)	76 (5.4)	464 (16.5)
TEAE leading to study withdrawal	32 (2.3)	7 (0.5)	39 (1.4)
TEAE leading to dose reduction	440 (31.3)	35 (2.5)	475 (16.9)
TEAE leading to hospitalisation	93 (6.6)	75 (5.3)	168 (6.0)
TEAE leading to dose hold	629 (44.7)	187 (13.3)	816 (29.0)
Label population			
Any TEAE	649 (98.0)	567 (86.3)	1,216 (92.2)
Grade 3 or 4 TEAE	327 (49.4)	76 (11.6)	403 (30.6)
Fatal TEAE	1 (0.2)	0 (0.0)	1 (0.1)
Serious TEAE (SAE)	45 (6.8)	36 (5.5)	81 (6.1)
Treatment-related TEAE	630 (95.2)	360 (54.8)	990 (75.1)
Serious Treatment-related TEAE	19 (2.9)	5 (0.8)	24 (1.8)
TEAE leading to treatment discontinuation	178 (26.9)	30 (4.6)	208 (15.8)
TEAE leading to study withdrawal	11 (1.7)	2 (0.3)	13 (1.0)
TEAE leading to dose reduction	203 (30.7)	13 (2.0)	216 (16.4)
TEAE leading to hospitalisation	41 (6.2)	35 (5.3)	76 (5.8)
TEAE leading to dose hold	280 (42.3)	75 (11.4)	355 (26.9)

Based on Tables 19 and 20 of the CS[1]
CS = company submission; ITT = intention-to-treat; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Table 4.11: Grade 1-4 TEAE in in ≥ 10%, label safety population from the ExteNET study

Adverse event	Neratinib (n=662)			Placebo (n=657)		
	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Diarrhoea	365 (55.1)	261 (39.4)	0	213 (32.4)	7 (1.1)	0
Nausea	280 (42.3)	9 (1.4)	0	135 (20.5)	2 (0.3)	0
Fatigue	177 (26.7)	13 (2.0)	0	129 (19.6)	2 (0.3)	0
Vomiting	150 (22.7)	24 (3.6)	0	41 (6.2)	2 (0.3)	0
Abdominal pain	145 (21.9)	11 (1.7)	0	58 (8.8)	1 (0.2)	0
Headache	119 (18.0)	6 (0.9)	0	125 (19.0)	1 (0.2)	0
Upper abdominal pain	90 (13.6)	6 (0.9)	0	35 (5.3)	3 (0.5)	0
Rash	90 (13.6)	3 (0.5)	0	40 (6.1)	0	0
Decreased appetite	79 (11.9)	1 (0.2)	0	13 (2.0)	0	0
Muscle spasms	81 (12.2)	0	0	21 (3.2)	1 (0.2)	0

Based on Table 22 of the CS [1]
CS = company submission; TEAE = treatment-emergent adverse event

Table 4.12: Characteristics of treatment-emergent diarrhoea in CONTROL compared with ExteNET

	Loperamide (n=137)	Budesonide + loperamide (n=64)	Colestipol + loperamide (n=120)	ExteNET neratinib arm (loperamide as needed) (n=1,408)
Median cumulative duration, days				
Any grade	14.0	24.0	16.0	59.0
Grade ≥ 2	5.0	6.0	3.5	10.0
Grade ≥ 3[a]	3.0	2.0	3.0	5.0[a]
Median diarrhoea episodes per patient				
Any grade	2	9	2.5	8
Grade ≥ 2	2	3	1	3
Grade ≥ 3[a]	1	1	1	2[a]
Action taken, %				
Dose hold	15.3	18.8	9.2	33.9
Dose reduction	7.3	3.1	4.2	26.4
Discontinuation	20.4	10.9	1.7	16.8
Hospitalisation	1.5	0	0	1.4

Based on CS Table 25[1]
[a] One grade 4 event in ExteNET safety population
CS = company submission

4.2.5 Ongoing trials

The CS reports that both studies are still in follow-up, with final data anticipated in the future. In the ExteNET trial, the OS survival is not yet mature and the final analysis will be conducted once

248 events have been reported. At the time of five-year analysis, 121 events had been reported over both treatment arms. Puma remains masked until the data reaches maturity ([redacted]). In light of this, the next anticipated publication date is not confirmed.

Data from the CONTROL trial are also not mature. Although the loperamide cohort have completed the study, ongoing are the cohorts for budesonide and colestipol. Additionally, a further three cohorts are in the process of recruiting. These additional cohorts will explore the safety profile of using loperamide as needed and initiating neratinib with a dose escalation. The new cohorts will investigate the following:

- neratinib + colestipol + loperamide as needed;
- neratinib dose escalation in cycle 1 + loperamide as needed, and
- neratinib dose escalation in cycle 2 + loperamide as needed.

A final analysis of the CONTROL study will be available after all patients have completed the 12 months of planned neratinib therapy. As these cohorts are still recruiting, the anticipated publication date cannot be confirmed.

ERG comment: The immaturity of study results of both, ExteNET and CONTROL, is a concern for the ERG, especially in regards to the interim analysis of the OS data for the label population in the ExteNET trial. In request for clarification, the ERG asked for an interim analysis of OS to be conducted. In response, the company stated that due to amendment 13 this analysis was no longer going to be conducted.[16] However, according to Table 6 of the CS, amendment 13 signifies an interim analysis at 124 events. Given that at the time of the ITT five-year analysis, 121 deaths had been reported across both treatment groups combined, the ERG believes an interim analysis of OS should have taken place for the CS.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company submission did not present an indirect comparison and/or multiple treatment comparison.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company submission did not present an indirect comparison and/or multiple treatment comparison.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

Below is a summary discussing the main areas of concerns for the ERG:

1. The NICE scope specified overall survival (OS) as on outcome. However, this outcome was not reported by treatment arm in the CS.[1] The CS did present a Kaplan-Meier curve of blinded OS for the HR+ population (Figure 13; page 64) but this did not contain results for each treatment group. The ERG asked for more recent OS results in the clarification letter but in their response the company stated that *"the only overall survival (OS) data currently available were presented in the dossier in Section B.2.6.13 in the OS subsection and include*

only the blinded OS data, as unblinding cannot occur until data reach maturity. While data for the ITT population will read out by [redacted], descriptive OS statistics for the HR+ subset are not expected to be available until [redacted]".[16] During the trial lifespan there have been 13 protocol amendments and the interim analysis of OS which was planned after 124 events was cancelled after global protocol amendment 13. One final analysis of OS is planned after 248 deaths. It is unclear why OS results for the HR+ subset will not be available until [redacted] when OS data for the full ITT population will be available in [redacted]. The HR+ patients are a subgroup of the ITT population so their results should be available at the same time. Without the full OS results for neratinib compared to placebo it is not possible to evaluate OS or include it in the economic model and this is a major limitation of the evidence presented by the company.

2. The ExteNET trial had invasive DFS (iDFS) as the primary outcome with disease-free survival including ductal carcinoma in situ (DFS-DCIS), and distant disease-free survival (DDFS) as secondary outcomes. Rather than having one outcome encompassing all types of progression in DFS, there were three different outcomes capturing DFS. The conclusions of the ExteNET trial for iDFS may not be applicable to overall DFS and need to be considered in the light of the fact that iDFS is a surrogate outcome for OS and the OS results are not available.[26] However, a systematic review published in 2019 included eight trials evaluating adjuvant treatment for HER-2 positive early breast cancer and analysed the association between DFS and OS using both patient- and trial-level data.[26] It found a strong association between DFS and OS with a treatment level association ≥ 0.75 suggesting that DFS may have good statistical validity to be used as a surrogate for OS in HER-2 positive early breast cancer, particularly following 12 months of treatment with trastuzumab. Overall, the ERG is uncertain to the extent to which iDFS translates into long-term OS benefits and whether iDFS is an acceptable surrogate for DFS as well as whether DFS is an acceptable surrogate outcome for OS in the label population. Furthermore, as detailed before, the definition of iDFS in the CS was narrower than the standard definition which might mean that relevant events could have been missed.

3. The ERG has some concerns regarding the applicability of both, the ExteNET study as well as the CONTROL study, to the UK. Only 41 participants from the UK (19 in the neratinib arm and 22 in the placebo arm) were part of the label population of ExteNET while *"CONTROL did not include any European sites"*.[21]

4. CONTROL is a sequential-cohort, open-label, phase II study with a small sample size, i.e. any results of this study should be considered with a degree of caution.

5. Given that non-English language articles were excluded during the screening process, potentially relevant studies might have been missed.

5. Cost effectiveness

5.1 ERG comment on company's review of cost effectiveness evidence

A single set of searches were undertaken to identify economic, cost and resource use and HRQoL evidence. The company submission and response to clarification provided sufficient details for the ERG to appraise the original literature searches and both sets of 2018 update searches. A good range of databases, conference proceedings and additional resources were searched.

5.1.1 Searches performed for cost effectiveness section

Sections B.3.1, B.3.4 and B.3.5 of the CS state that the systematic literature review (SLR) described in Appendix G was designed to identify all economic, utility, and resource-use studies of HER2+ breast cancer.[21] This section contains summaries and critiques of these searches. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[19] The submission was checked against the single technology appraisal (STA) template for company/sponsor submission of evidence.[20] The ERG has presented only the major limitations of the search strategies in the main report. Further minor comments can be found in Appendix 1.

Appendix G.1 of the CS states that MEDLINE and MEDLINE in Process (PubMed), Embase (Elsevier platform), Biosis (Dialog platform), DARE, NHS Economic Evaluations Database (EED) and the HTA Database (via the Cochrane Library) and EconLit were searched to identify utility, resource-use and cost data, as well as published articles of economic models in HER2+ breast cancer. All search strategies were reported in detail in Appendix G.1.[21] The original searches were conducted on 25 October 2016, with update searches taking place on 19-20 February 2018 and 21 November 2018. The electronic database searches were limited to articles published in English, German, or French. Databases were reported to have been searched from inception, although specific start dates were not provided.

Searches were conducted and reported for conference proceedings from 2015-2018 for the following conferences: International Society for Pharmacoeconomics and Outcomes Research, American Society of Clinical Oncology, European Society for Medical Oncology, European Breast Cancer Conference, St. Gallen International Breast Cancer Conference, San Antonio Breast Cancer Symposium.

Reference lists of included economic analyses, systematic reviews, and HTA reports were searched to identify further relevant studies. In addition, the following key international HTA and health economics websites were searched to identify HTA reports in early HER2+ breast cancer: NICE, Scottish Medicines Consortium (SMC), CADTH, Haute Autorité de Santé (HAS), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) and the Cost effectiveness Analysis (CEA) Registry.

ERG comment:

- The selection of databases searched was adequate, and overall the searches were clearly reported and reproducible. The database name, host and date searched were provided. An extensive range of resources additional to database searches was included in the SLR to identify further relevant studies and grey literature.
- Study design filters to identify economic evaluations, health state utility data and cost and healthcare resource data were applied. The filters were not referenced, so it was unclear

whether they were published objectively-derived filters. The filters contained a combination of subject heading terms (MeSH and Emtree) and free text terms, and the ERG deemed them to be adequate.

- The economic evaluation, cost and utility facets used in the NHS EED and EconLit searches were unnecessary, given that these databases only contain economics literature. The ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits used. However, given the range of additional resources used in the SLR, it is unlikely that any relevant studies have been missed.
- The strategies used to search conferences, trials registers and other resources for economic evaluations, health state utility data and cost and healthcare resource data were not provided. The CS states: ' Search terms for the searches performed on the online resources were taken from those listed in Appendix G.1.2, as appropriate for the search features of individual sites' (Appendix G; p120). These searches were therefore not reproducible.
- The ERG was concerned that limiting the searches to English, French and German language may have introduced potential language bias. Current best practice states that "Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication".[28]

5.1.2 Inclusion/exclusion criteria

Inclusion/exclusion criteria applied for the SLR to identify the economic evaluations were provided in Table 32 in Appendix G of the CS.[21] Inclusion/exclusion criteria were sensibly based on the PICOS criteria, to identify the Population and disease, Interventions, Comparators, Outcomes, and Study types of interest. The ERG considers restrictive the criterion to exclude cost studies reporting resource use estimates or costs not in France, Germany, or the UK. Studies performed in other countries could potentially contribute relevant information as well and adjustments to costs can be made to enhance their transferability. Also, the ERG considers restrictive the exclusion of studies reporting HRQoL data measured by a disease-specific tool (instead of a generic tool) since such studies can still provide relevant information for which the disease-specific HRQoL data can be mapped to generic HRQoL.

5.1.3 Identified studies

The cost effectiveness SLR search strategy resulted in 1,532 unique abstracts being identified and screened. Of these, 187 were considered potentially relevant and were read at full text. Twenty-eight papers were included, of which 21 were economic evaluation studies (of which four were HTAs), five utility studies and two healthcare cost and resource-use studies in the adjuvant or extended adjuvant setting. The PRISMA diagram for this SLR is shown in Figure 3 in Appendix G of the CS.[21]

Table 33 in Appendix G.3 presents a summary of the included HTAs, of which two are NICE appraisals and two are from the SMC.[21] All pertain to adjuvant treatment of trastuzumab or pertuzumab plus trastuzumab in early stage HER2+ breast cancer. Table 34 in Appendix G.3 presents summaries of the identified economic evaluation studies, based on breast cancer populations in UK and European as well as Australia, Canada, the USA, and Thailand.[21]

The SLR identified five studies reporting health-state utility estimates in patients with HER2+ breast cancer. The results of these five studies were summarised in Table 43 in Appendix H.[21] In Table 44 in Appendix H, the company provided an assessment of the extent to which they believe these utility studies comply with the NICE reference case. Any utility estimates identified in the included economic evaluation studies (those published at full test) were also extracted and summarised in

Table 45 in Appendix H.[21] Table 46 in Appendix H presents a summary of the values which the company suggest may be appropriate for an economic model of neratinib.[21]

The SLR identified two studies reporting resource utilisation and/or costs in patients with HER2+ breast cancer, which are summarised in Table 47 in Appendix G.2.[21] Relevant cost data were also extracted from included economic evaluations (full text publications only), an overview of which is provided in Table 48 in Appendix G.2.[21] More detailed summaries of cost and resource use data identified are provided for countries of interest (UK, France and Germany) in Table 49 and other countries in Table 50 in Appendix G.2.[21]

ERG comment: The SLR search for utilities did not identify either of the utility studies that were included in the model. The Lidgren et al. 2007 study was identified from extracting utility data from identified published economic evaluation studies.[29] In section B 3.4.3.1 of the company submission,[1] the company stated that the Lloyd et al. 2006 study was identified through additional reviews of recent NICE submissions in similar indications,[30] which were used to inform the selection of utility values in metastatic recurrence, which was outside the scope of the SLR. However, the included Lidgren et al. 2007 study provided values for distant recurrence, so it is unclear why the company felt the need to include additional sources beyond the scope of the review.

5.1.4 Interpretation of the review

In the absence of a prior economic evaluation of neratinib, a *de novo* economic model was developed by the company. The current model was was similar to the model developed for the appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer.[25] The main differences and similarities between the economic model used for the current submission and the model used for the pertuzumab appraisal are described in section 5.2.2 of this report.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

A summary of the economic evaluation conducted by the company is presented in Table 5.1.

Table 5.1: Summary of the company submission economic evaluation

	Approach	Source/Justification	Signpost (location in ERG report)
Model	A Markov model with five health states was used to assess the cost effectiveness of neratinib. It considered a 55-year (lifetime) time horizon, and was assumed to capture all relevant costs and benefits associated with the introduction of neratinib in England and Wales.	The conceptual model is similar to the model developed for TA569.[25] The choice of the time horizon (55 years) seems appropriate since all patients in the simulation die before reaching the time horizon.	Section 5.2.2
States and events	There are five health states included in the model: 1) iDFS (invasive Disease-Free Survival), 2) Local recurrence, 3) Remission, 4) Distant recurrence, and 5) Dead. In short, patients remain in iDFS until they experience a (Local or Distant) recurrence, or die from general population mortality. Following Local recurrence, patients go through a tunnel state (for 1 year) before transitioning to either Remission or Dead from general population mortality. After Remission, patients either progress to Distant recurrence, or die from general population mortality. Patients can also transition from iDFS to distant recurrence. From distant recurrence, patients transition to Dead according to post distant recurrence mortality.	The five health states represent the primary stages of disease in early-stage breast cancer and correspond to the primary and secondary endpoints in the ExteNET trial. The model structure allows for variation in risk of recurrence and death over the time horizon. The assumption that all patients who die from breast cancer first move through Distant recurrence is in alignment with TA569, which also applies to the assumption that patients in Remission will either progress to Distant recurrence or die from general population mortality.[25] The probabilities for transitioning from Remission to Distant recurrence are assumed to be the same, and are also used in TA569 and TA424.[25, 31] Also in alignment with TA569 are the assumptions that general population mortality applies to all health states except distant recurrence, and that patients stay in local recurrence for 1 year.[25]	Section 5.2.2
Comparators	The comparator is placebo.	Currently no other treatment is available for people with HR+/HER2+ breast cancer in the extended adjuvant setting after 1 year of treatment with trastuzumab.	Section 5.2.4
Natural history	Breast cancers are distinguished by the tumour-node-metastasis (TNM) staging system and molecular biomarkers, which		Section 2.1

	Approach	Source/Justification	Signpost (location in ERG report)
	can be used to drive prognosis and treatment-related decisions.[3-5]Such molecular biomarkers include HR+, HER2+, oestrogen (ER+), or progesterone (PR+),[1] specifically ER+ and PR+ which can induce breast tissue growth or change as a response method to the changing hormone levels.[6, 7]The dominant driver to the development of breast cancer tumours is the overexpression of the HER2 oncogene which can influence the metabolic functions of the tumour cells, enable cell survival, induce cell proliferation, and increase invasiveness.[8, 9] When patients have HR+/HER2+ breast cancer, this indicates the tumours co-express hormone receptors (HRs, which could be ER and/or PR) and HER2.[1] Such a co-expression then modifies the tumour response to both HER2-directed and hormonal therapies.[1]		
Treatment effectiveness	Treatment effectiveness was based on the results from (a subpopulation that matches the label population of) the ExteNET trial. In addition, the impact of prophylaxis on the incidence and duration of diarrhoea was based on the CONTROL trial. In the absence of data on overall survival (OS) per treatment arm, treatment effectiveness is based on iDFS.	[redacted].	Section 5.2.6
Adverse events	The following adverse events (AEs) were taken into account: diarrhoea (grade 1 /2 and grade 3 /4), vomiting, nausea, abdominal pain, fatigue, and increased alanine aminotransferase.	The effects of AEs are captured by applying a utility decrement over a stated time period based on data from ExteNET, and for the effect of prophylaxis for diarrhoea based on data from CONTROL. Utility decrement values were selected from prior NICE appraisals or published literature.	Section 5.2.7
Health related QoL	HRQoL data from the ExteNET trial is only available for the iDFS health state, and is based on an incomplete dataset that was analysed using a model that produced inconsistent results. Utility values for health states other than iDFS (and Remission, which was assumed to be the same) are based on published literature.	The collection of HRQoL in ExteNET was ceased following a protocol amendment. Therefore, HRQoL data were incomplete due to cases with missing values and no data were available for patients experiencing a recurrence.	Section 5.2.8

	Approach	Source/Justification	Signpost (location in ERG report)
Resource utilisation and costs	The model included treatment costs for neratinib, diarrhoea prophylaxis, monitoring costs (incl. GP visits and liver function tests), costs associated with AEs, and costs of adjuvant and/or subsequent treatments.	Unit costs were obtained from the PSSRU 2018,[32] NHS reference costs[33] and the NICE clinical guideline for familial breast cancer (CG164).[34] Drug costs were taken from the BNF and eMIT. Frequency of resource use was based on estimates from the NICE pertuzumab appraisal (TA569).[25] Resource use associated with the additional monitoring required for neratinib patients was based on expert opinion[35] and the SmPC for neratinib.[36] AE costs were taken from the PSSRU 2018,[32] NHS reference costs[33] and previous technology appraisals TA465[37] and TA347[38].	Section 5.2.9
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case.	Section 5.2.5
Sensitivity analysis	Probabilistic and one-way sensitivity analysis.	According to NICE reference case.	Section 5.2.12

AE = adverse event; BNF = British National Formulary; CG = clinical guidance; eMIT = electronic Market Information Tool; ER+ = Oestrogen receptor-positive; ERG = Evidence Review Group; GP = general practitioner; HER2+ = human epidermal growth factor receptor 2-positive; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive; HRQoL = health related quality of life; iDFS = invasive disease-free survival; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PR+ = Progesterone receptor-positive; PSS = Personal Social Services; PSSRU = Personal Social Services Research Unit; QALY = quality adjusted life year; SmPC = Summary of Product Characteristics; TA = technology appraisal; TNM = Tumour-Node-Metastasis

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.2: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Outcome measures included in the CS: • iDFS (invasive disease-free survival) • Post-distant recurrence mortality • Adverse effects of treatment (ExteNET label population data used for all non-diarrhoea AEs and diarrhoea AEs without prophylaxis. CONTROL label population data for loperamide group used for diarrhoea AEs with prophylaxis) • Health-related quality of life Not included in the CS: • Treatment-specific OS: ExteNET data for label population will only be available from [redacted]
Perspective on costs	NHS and PSS	According to NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	According to NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Time horizon can be considered lifetime (model time horizon of 55 years for cohort with mean age of 51.2 years at baseline)
Synthesis of evidence on health effects	Based on systematic review	Systematic literature reviews were conducted for relevant cost effectiveness studies, and studies on HRQoL, cost and resource utilisation for the target population.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	According to NICE reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	HRQoL data were derived from the ExteNET (only for iDFS), for the proportion of patients experiencing AEs (all non-diarrhoea AEs and diarrhoea AEs without prophylaxis), and for the duration of AEs) and the CONTROL (the proportion of patients experiencing diarrhoea AEs with prophylaxis, and for the duration of AEs in case of prophylaxis for diarrhoea) trials. HRQoL data for other aspects were based on assumptions,

		previous TAs, or literature.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	HRQoL data for iDFS (and remission, which was assumed to be equal to iDFS) were based on ExteNET, for other health states on previous TAs or literature, and for AEs on ExteNET (all non-diarrhoea AEs and diarrhoea AEs without prophylaxis) and CONTROL (diarrhoea with prophylaxis).
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	According to NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	According to NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	According to NICE reference case

AE = adverse event; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; iDFS = invasive disease-free survival; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PSS = personal social services; QALY = quality-adjusted life year; TA = technology appraisal; UK = United Kingdom

5.2.2 Model structure

The company developed a *de novo* five-health-state Markov model to evaluate the cost effectiveness of neratinib compared to standard treatment with no further HER2-directed therapy. The structure of the model was similar to that of the NICE appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer.[25]

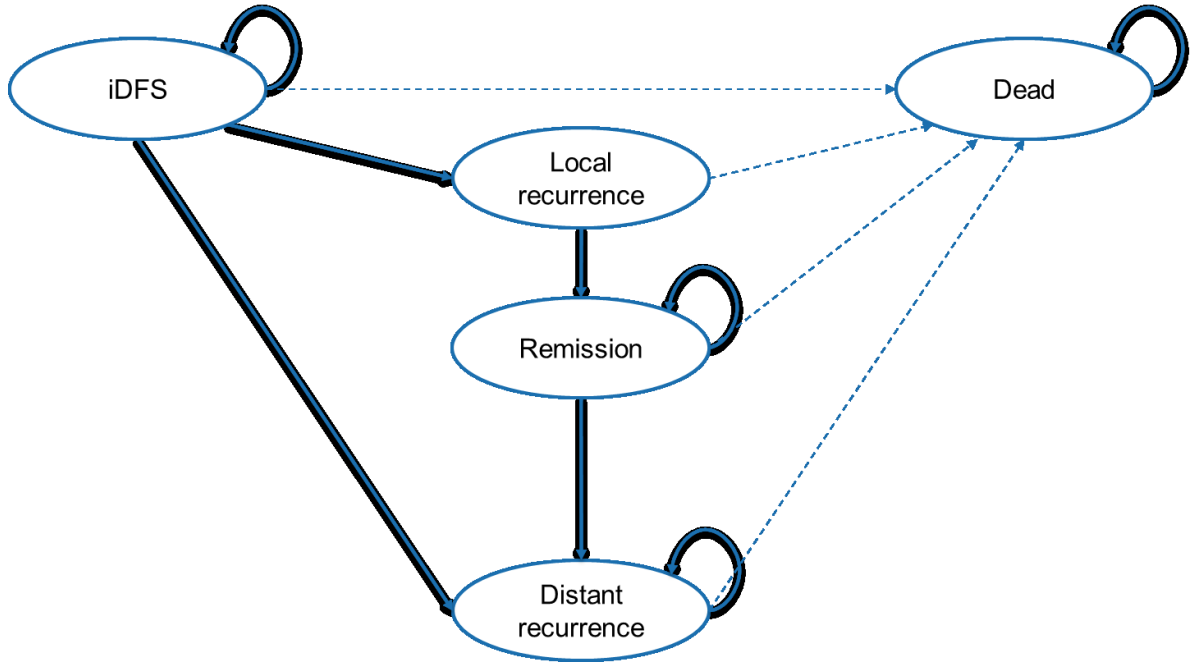
According to the company, the health states included in the model represent the primary stages of disease in early-stage breast cancer (disease free, local recurrence, remission, distant recurrence and dead) and correspond to the primary and secondary endpoints in the ExteNET trial as discussed in section 4.2 of this report. The primary endpoint for the ExteNET trial was iDFS, which was defined as the time from randomisation to the first occurrence of one of the following events: 1) Invasive ipsilateral breast tumour recurrence, 2) Local/regional invasive recurrence, 3) Distant recurrence, 4) Death from any cause, 5) Invasive contralateral breast cancer. Invasive ipsilateral breast tumour recurrence and invasive contralateral breast cancer were included as part of the local recurrence health state in the model. The structure of the conceptual model is shown in Figure 5.1.

Patients start the simulation in the iDFS health state where they receive neratinib or standard treatment. From the iDFS health state, patients can transition to local recurrence, distant recurrence or dead. Local recurrence is a tunnel health state in which patients receive adjuvant therapy until they transition to remission or death. Patients who transitioned to remission can stay in that health state, or

move to distant recurrence or death. From all health states, patients can transition to death. From iDFS, local recurrence and remission, patients die according to general population mortality risks. Mortality from the distant recurrence health state was modelled assuming the post distant recurrence mortality risk (based on blinded survival data) obtained from both arms of the ExteNET trial, as mentioned in section 4.2 of this report. Thus, the company assumed that all breast cancer deaths occur from the distant recurrence health state.

Costs and utilities allocated to the health states of the model (except dead) are used to calculate expected total costs and total quality-adjusted life years (QALYs) per model cycle (one month). Half-cycle correction was applied to these calculations.

Figure 5.1: Model structure



Based on Figure 26 of the CS.[1] Abbreviation:
CS = company submission; iDFS = invasive disease-free survival

ERG comment: A traditional partitioned survival analysis approach was initially considered by the company. However, since OS data were not available by treatment arm, the company decided to follow an approach similar to that taken in the NICE appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer.[25] The main differences and similarities between the economic model used for the current submission and the model used for the pertuzumab appraisal (TA569) were provided in response to the clarification letter (question B5).[16] These are summarised below:

- A *de novo* model was developed for the current submission. Where possible, all input data in the model are reflective of the neratinib label population.
- Given the similar clinical pathway for the patient populations in TA569 and ExteNET, the model used in the company submission for TA569, as well as the input provided by the ERG and the committee, were considered by the company to develop the current model.[25]
- The input received from one clinical expert, confirmed that the treatments for treating local and distant recurrence following neratinib were expected to be similar to the treatments and proportions of treatments used in TA569 (see Appendix M of the CS[21]).

- Given the similar clinical pathway for patient populations in TA569 and the ExteNET trial, resource use data were aligned with TA569, as were subsequent treatments received in local and distant recurrence.[25]
- Adjustments were made to the iDFS health state, where the first-year values from TA569 were removed as in this submission patients receiving neratinib will be one year further in their treatment and will have finished their course of trastuzumab.[25]
- Monitoring costs related to neratinib were included in the model, based on clinical input received.
- Other health state costs were assumed to reflect recurrence, remission, local recurrence, and distant recurrence, which would be generalizable between the populations in TA569 and ExteNET.[25]
- In TA569, patients in iDFS were split across two health states; iDFS on-treatment and iDFS off-treatment. The model for this submission has only one health state for iDFS, since all patients will have concluded prior treatment (with the exception of endocrine therapy) and, therefore, this subdivision was not deemed required by the company.[25]
- The metastatic setting (distant recurrence) is split into first- and second-line treatment in TA569.[25] Transition probabilities were derived from studies of subsequent lines of therapy. This approach was criticised by the ERG for TA569 that argued it would have been better to utilise the evidence collected in the clinical trials for pertuzumab in adjuvant therapy of early HER2-postive breast cancer. Based on this criticism, and the fact that neratinib is not approved in metastatic breast cancer (and, therefore, subsequent treatment will not be influenced by neratinib treatment for early breast cancer), the company decided not to model individual lines of therapy for distant recurrence in the neratinib model. Instead of that, the model uses post progression survival data from ExteNET.
- The model in TA569 modelled post progression survival using an exponential distribution, in order to simplify the model structure regrading time-dependent probabilities.[25] The neratinib model does not have this limitation and allows for time-dependent probabilities (i.e. distributions other than the exponential) to model post progression survival.
- The survival extrapolations for DFS used in the pertuzumab model in TA569 did not provide a good fit when compared with that of the HERA trial.[25] Thus, the model incorporated a cure fraction to allow for patients to transition on to general population mortality. However, there were concerns raised about this concept during the assessment. The extrapolation of iDFS in the current model did not have a similar issue with regards to iDFS predictions and, in fact, the model allows for the incorporation of the HERA data to inform the survival extrapolation as a scenario. Therefore, a cure fraction was not incorporated in the current model as the current extrapolations of the trial data are believed to represent long-term iDFS adequately without needing any correction factors.

The limitations discussed in the clinical effectiveness sections (and summarised in section 4.6) also apply here. These mostly concern the absence of OS data (per treatment arm) and the narrower definition used for iDFS which has been used as a surrogate for DFS.

5.2.3 Population

The population considered in the economic evaluation is adult patients with early stage HR+, HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab-based therapy, as described in section B.3.2.1 of the CS.[1]

ERG comment: The population considered by the company in the economic evaluation is consistent with a subgroup of the study population of ExteNET and neratinib's full marketing authorisation, as described by the decision problem presented in section B.1.1 of the CS.[1] Some concerns regarding the applicability of the ExteNET trial results to the UK setting were discussed in section 4.2.3 of this report. In particular, Figure 4.2 presented the five-year DFS in HR+ participants of the ITT population who had prior adjuvant trastuzumab ≤ 1 year (label population). The DFS hazard ratio for all patients was 0.58 (95% CI 0.41 to 0.82) whereas for Western European patients this hazard ratio was equal to 0.70 (95% CI 0.41 to 1.16). In the economic model, iDFS curves were fitted based on data from all patients in the label population, as will be explained in section 5.2.6.1. A subgroup analysis based on the Western European label population would have been of interest since this could have been more representative for the UK population. However, such analysis was not possible with the current version of the economic model.

5.2.4 Interventions and comparators

The intervention considered in the cost effectiveness analyses is neratinib within its label population. Therefore, neratinib is expected to be administered orally at a recommended dose of 240 mg, as 6×40 mg tablets taken once daily and continually for one year. The comparator considered in the economic analysis is standard treatment with no further HER2-directed therapy. Standard treatment is defined as placebo in the ExteNET trial.[6]

5.2.5 Perspective, time horizon and discounting

Although not explicitly mentioned in the company submission, the economic analyses were conducted from the perspective of the NHS and Personal Social Services (PSS). The economic model considered a 55-year horizon, which is long enough to be considered as lifetime. Costs and QALYs were discounted at 3.5% per annum according to the NICE method guidance.[39]

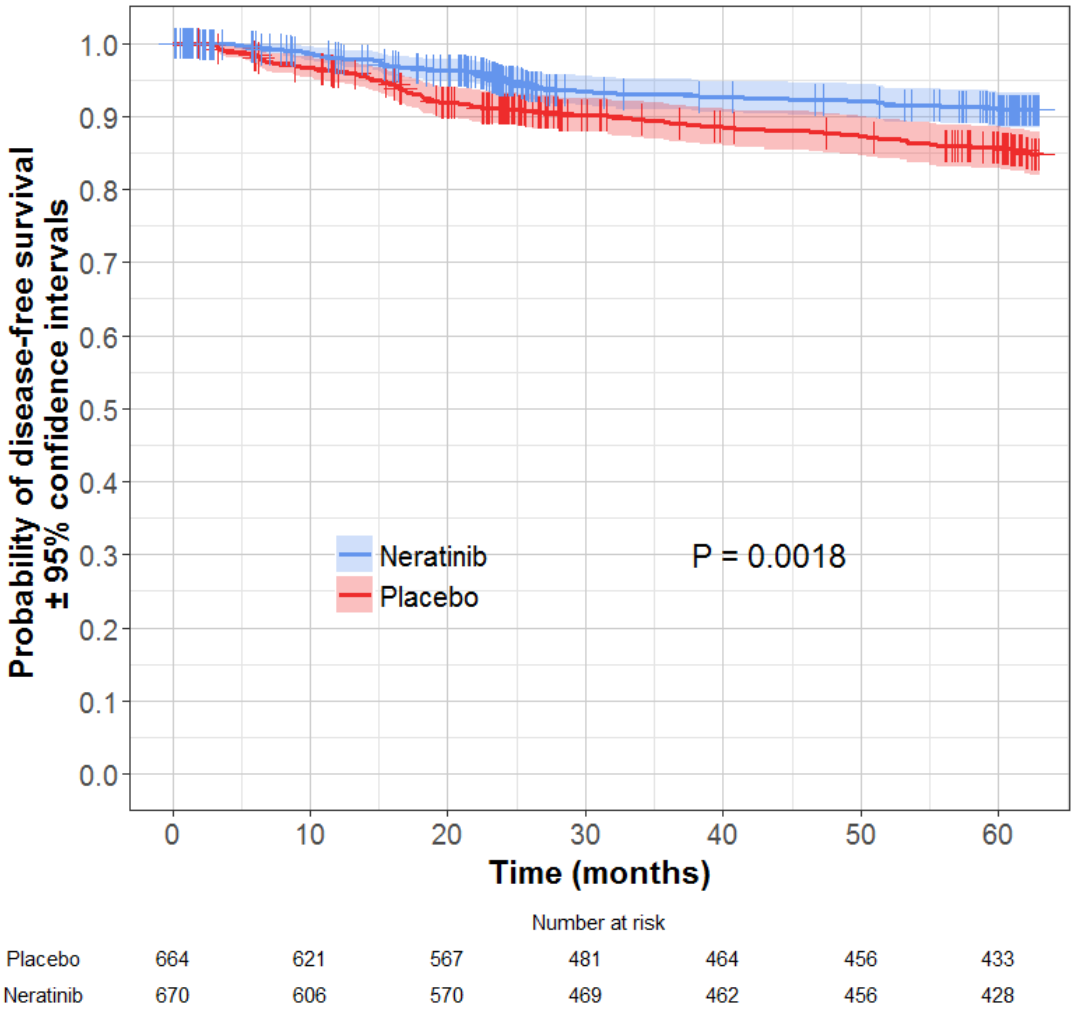
5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Invasive disease-free survival

Assessing the proportional hazards assumption between the treatment arms in ExteNET

The iDFS Kaplan-Meier (KM) curves for the two study arms in the ExteNET trial (for patients with HR+ breast cancer) can be seen in Figure 5.2. This figure suggests a treatment effect associated with neratinib. Based on these survival data, the company performed a log-rank test and the result (p-value = 0.0018) indicated that iDFS was statistically significantly different between the two arms.

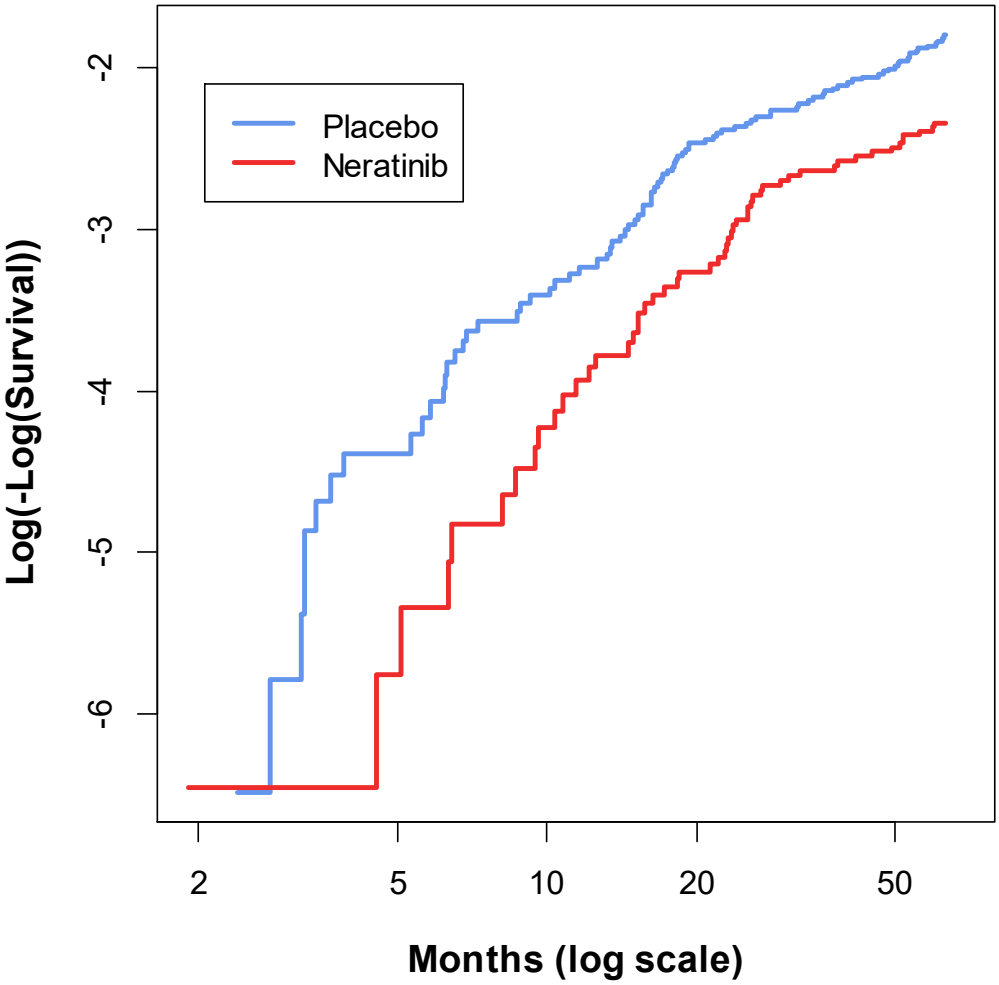
Figure 5.2: Kaplan-Meier estimates of iDFS from ExteNET: trastuzumab therapy completed within the past 12 months: HR+



Based on Figure 9 in Appendix L of the CS[21]
CS = company submission; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive; iDFS = invasive disease-free survival

Subsequently, the company investigated whether this treatment effect on iDFS could be modelled assuming proportional hazards between the neratinib and placebo arms. The Therneau-Grambsch test for non-proportional hazards (null hypothesis = proportional hazards holds) was performed on the iDFS data from ExteNET and the result was not significant (p-value = 0.575). Thus, with the current data, the null hypothesis (proportional hazards for iDFS) could not be rejected. To support this assumption, the company presented the log-(log) survival plot shown in Figure 5.3. Based on this plot, the company concluded that the proportional hazards assumption was met since the two lines seem to be (approximately) parallel.

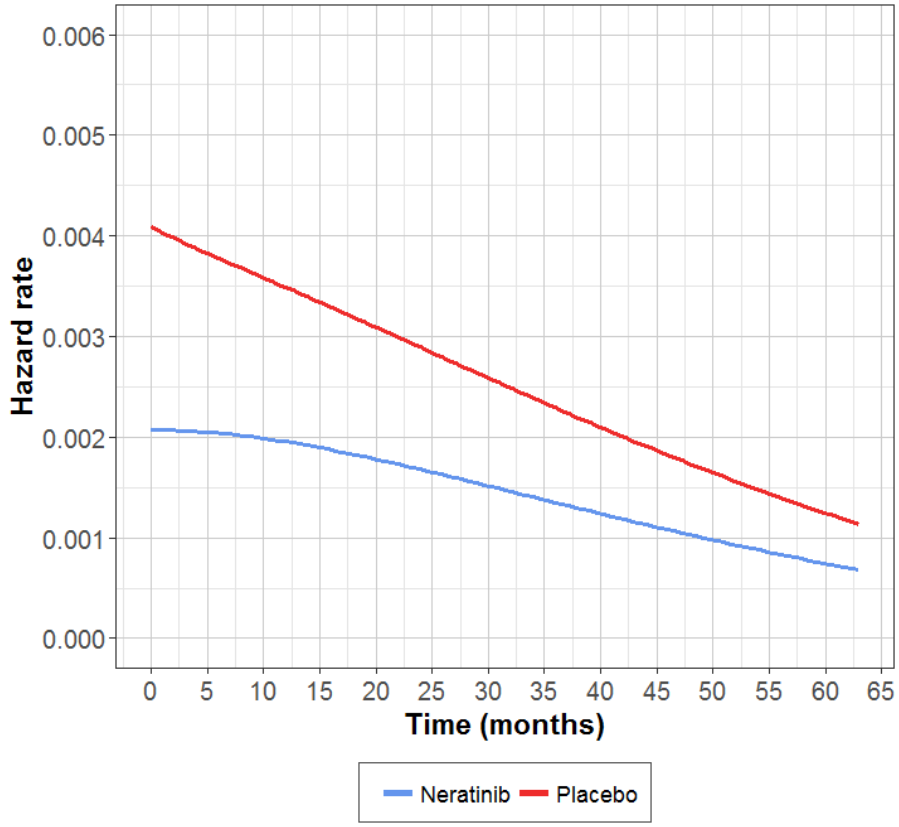
Figure 5.3: iDFS log-(log) survival plot from ExteNET: trastuzumab therapy completed within the past 12 months: HR+



Based on Figure 10 in Appendix L of the CS[21]
CS = company submission; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive; iDFS = invasive disease-free survival

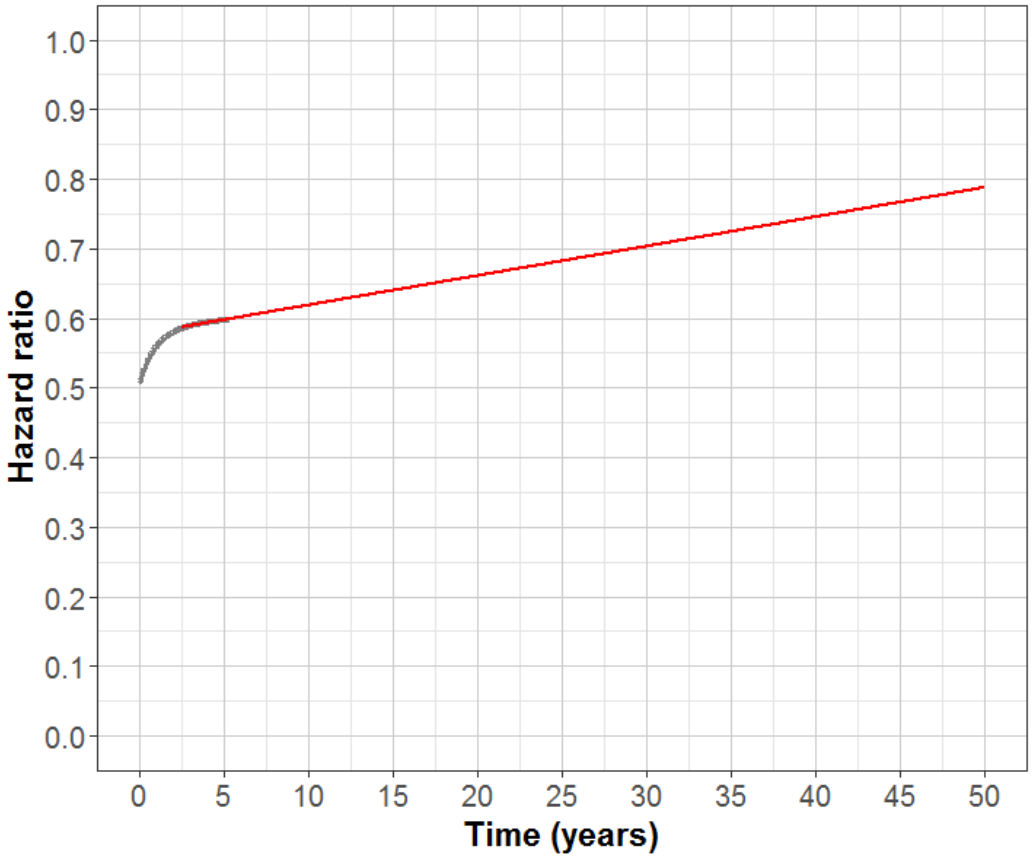
The iDFS (smoothed) hazard rates for the label population in ExteNET are shown in Figure 5.4. It can be seen that both hazard rates are decreasing and getting closer to each other in time. Moreover, Figure 5.5 shows the hazard ratio estimated from those smoothed hazard rates. It is clear that the hazard ratio (even before linear extrapolation – so from year 0 to 5) is not constant. These two plots suggest that the proportional hazards assumption for iDFS in ExteNET does not hold.

Figure 5.4: Smoothed hazard rates for iDFS from ExteNET data: prior trastuzumab in HR+ population



Based on Figure 32 of the CS[1]
CS = company submission; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive; iDFS = invasive disease-free survival

Figure 5.5: Hazard ratio for iDFS from ExteNET data: prior trastuzumab in HR+ population



Based on Figure 33 of the CS[1]
CS = company submission; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive; iDFS = invasive disease-free survival

ERG comment: The analyses of iDFS proportional hazards presented by the company resulted in opposite conclusions. However, the company concluded that there was no evidence against the proportional hazard assumption for iDFS. This conclusion was based on the result of the Therneau-Grambsch statistical test and the assessment of the log-(log) survival plot in Figure 5.3. The ERG does not agree with this conclusion for the reasons summarised below:

- Statistical test: misinterpretation of the p-value. Not rejecting the null hypothesis of the test does not automatically imply that it will hold in reality.[40]
- The company ignored part of the results provided within the submission, which resulted in a biased assessment. The analysis of the hazard rates and the hazard ratio in Figures 5.4 and 5.5 clearly suggest that the proportional hazard assumption does not hold for iDFS (e.g. the hazard ratio is not constant over time).
- The company indicated in Appendix L of the CS that different approaches to smoothing hazard rates may produce different conclusions.[21] Therefore, to gain insight into this point, the ERG asked the company (see clarification question B10c) to explore different approaches to smoothing the hazard rates for the label population and compare their conclusions.[41] Unfortunately, these analyses were not provided by the company.[16]

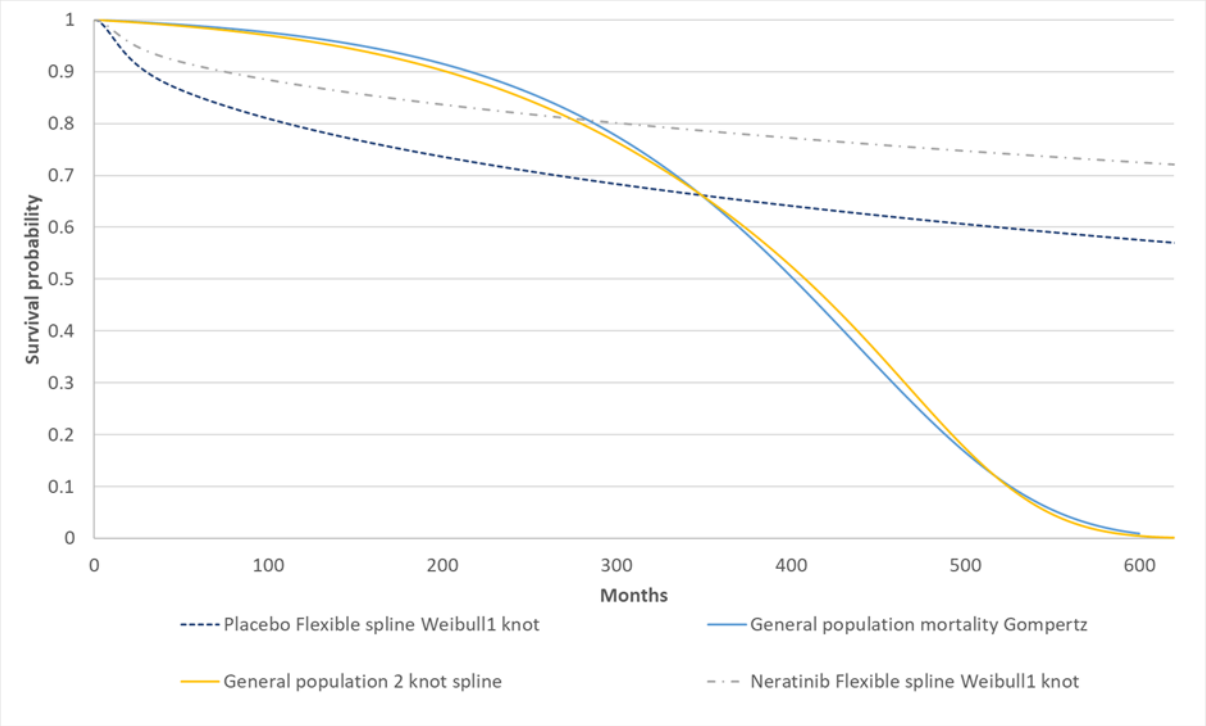
In conclusion, the ERG considers that, at least, there is uncertainty regarding the assumption of proportional hazards for iDFS and, therefore, other options should have been considered in the economic analyses as well.

Assuming proportional hazards for iDFS has an impact on two main drivers of the model: 1) the type of treatment effect and 2) the selection of parametric survival models to extrapolate iDFS. Regarding the treatment effect, the company assumed for the base-case analysis that the treatment effect observed at the end of the five-year follow-up was maintained until the patients had equal risk of an iDFS event as the general population. A more rapid waning in the treatment effect was explored in additional scenarios though. As mentioned above, and further explained in the next subsections, the ERG does not agree with the company's choice and considers that a more rapid waning in the treatment effect is more plausible. The second consequence, as will be seen next, is that non-proportional hazard parametric models (to extrapolate iDFS) were not considered in the economic analyses conducted by the company. The ERG considers that the selection of parametric models should have been broader and should have included both proportional and non-proportional hazards models. The impact of choosing non-proportional hazards models on the economic results was explored by the ERG in section 7 of this report.

Fitting and selection of parametric survival models

In the base-case analysis, the company modelled iDFS using data from the ExteNET trial in combination with general population survival data. The inclusion of general population survival data was needed due to the immaturity of the ExteNET data, which resulted in implausible extrapolations of long-term survival curves. As shown in Figure 5.6, the extrapolated survival curves from ExteNET resulted, in the long-term, in a greater survival than the general population.

Figure 5.6: Survival curves for iDFS ExteNET data and general population survival data



Based on Figure 27 of the CS[1]

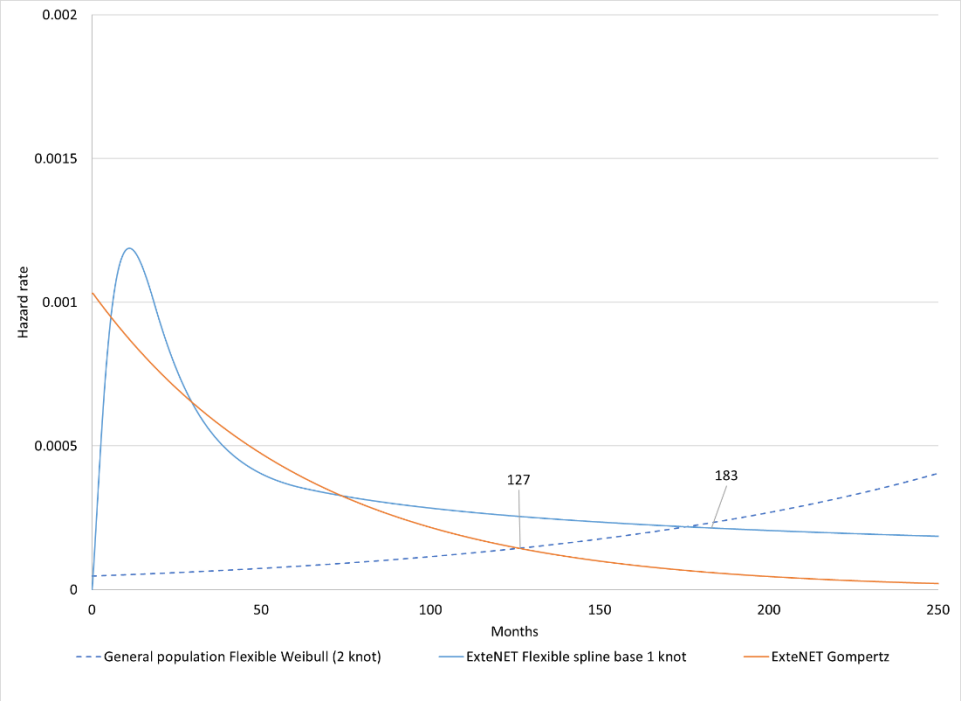
CS = company submission; iDFS = invasive disease-free survival

Parametric functions were fit to the ExteNET data following the recommendations of the Decision Support Unit (DSU) guidelines.[42] These parametric functions were used to model hazard rates over time from which survival probabilities were derived. Since the company considered that proportional hazards for iDFS could be assumed, a pooled survival model, with a covariate for treatment effect, was used to fit parametric survival models to the ExteNET iDFS data. The Akaike information

criterion (AIC), Bayesian information criterion (BIC) and Integrated Brier score (IBS) goodness-of-fit statistics, and visual inspection of the extrapolated curves compared with the Kaplan-Meier curves obtained from ExteNET, were used by the company to choose among various parametric survival models. For the base-case analysis, the company chose a flexible-spline Weibull (with one knot) to model iDFS and the same distribution, but with two knots, to model general population mortality. In scenario analyses, a Gompertz distribution was used to model both iDFS and the general population mortality.

As mentioned above, general population survival data were used to avoid implausible extrapolations of the ExteNET survival curves. Thus, at a certain time cycle, patients in the model "switch" from the ExteNET iDFS hazard rate to the general population mortality hazard rate. The switching point is obtained when the two hazard rates cross so that it is assumed that the ExteNET hazard rate cannot be lower than the general population hazard rate. The switching point depends on the parametric curves chosen to model iDFS in the placebo and neratinib arm, and to model mortality in the general population. An example for the placebo arm can be seen in Figure 5.7.

Figure 5.7: Hazard rates – placebo arm iDFS ExteNET and general population mortality



Based on Figure 31 of the CS[1]
CS = company submission; iDFS = invasive disease-free survival

The company intended to use a third dataset, from the HERA trial,[43] to extrapolate iDFS after the ExteNET trial follow-up. However, after performing all analyses, the company noted that the survival predictions based on the ExteNET and general population data only were nearly the same as the predictions including HERA data. For simplicity's sake, HERA data were not included in the base-case extrapolation analysis but it was used in scenario analyses and for validation purposes. Further details can be found in Appendix L of the CS.[21]

ERG comment: The company presented in Appendix L comprehensive survival analyses to fit parametric functions to the ExteNET iDFS data.[21] These analyses were methodologically well performed, followed the recommendations of the DSU guidelines,[42] and included a large number of parametric functions (both proportional and non-proportional hazards models). However, as

previously criticised, the ERG considers that the final selection of parametric models was insufficient and should have not been restricted to proportional hazards models only.

As mentioned above, parametric models were chosen based on visual inspection of the extrapolated curves compared with the KM curves obtained from ExteNET and several goodness-of-fit statistics (AIC, BIC and IBS). Figures 5.8 and Figure 5.9 show the extrapolated iDFS curves (compared with the KM curves) from the parametric models considered by the company. Note that these curves also include "stratified" models, which means that two different curves were separately fitted to each treatment arm (as opposed to one pooled survival model with a covariate for treatment effect, which would implicitly imply proportional hazards). The company assessed the goodness of fit based on these curves as follows:

- Gompertz and stratified[1] generalised gamma models appeared to give a good visual fit with the Kaplan-Meier estimates.
- Flexible spline–based Weibull models gave a good visual fit with the data.
- Exponential, Weibull, stratified Weibull, lognormal, log-logistic, and stratified log-logistic models did not appear to have as good a visual fit to the midsection of the Kaplan-Meier estimates but had a reasonable fit to the early and late part of the data.
- Generalised gamma did not appear to fit the data well at the end of the trial follow-up and therefore may not produce accurate extrapolations beyond the clinical trial data.

Given the lack of clarity, the ERG finds it difficult to make assessments based on these two figures, or even based on the individual figures – with a larger format – as can be seen in Appendix 2 of this report. In particular, it is difficult to discard any distributions as potential candidates to model iDFS.

[1] In the company submission only the generalised Gamma distribution is mentioned. However, as can be seen below, the company indicated that the generalised Gamma did not fit well at the end of the trial follow-up, which seems to be more in line with Figure 5.8. Therefore, the ERG believes that this statement in the company submission refers to the stratified distribution.

Figure 5.8: Standard parametric models fitted to the ExteNET trial data: disease-free survival: trastuzumab therapy completed within the past 12 months: HR+

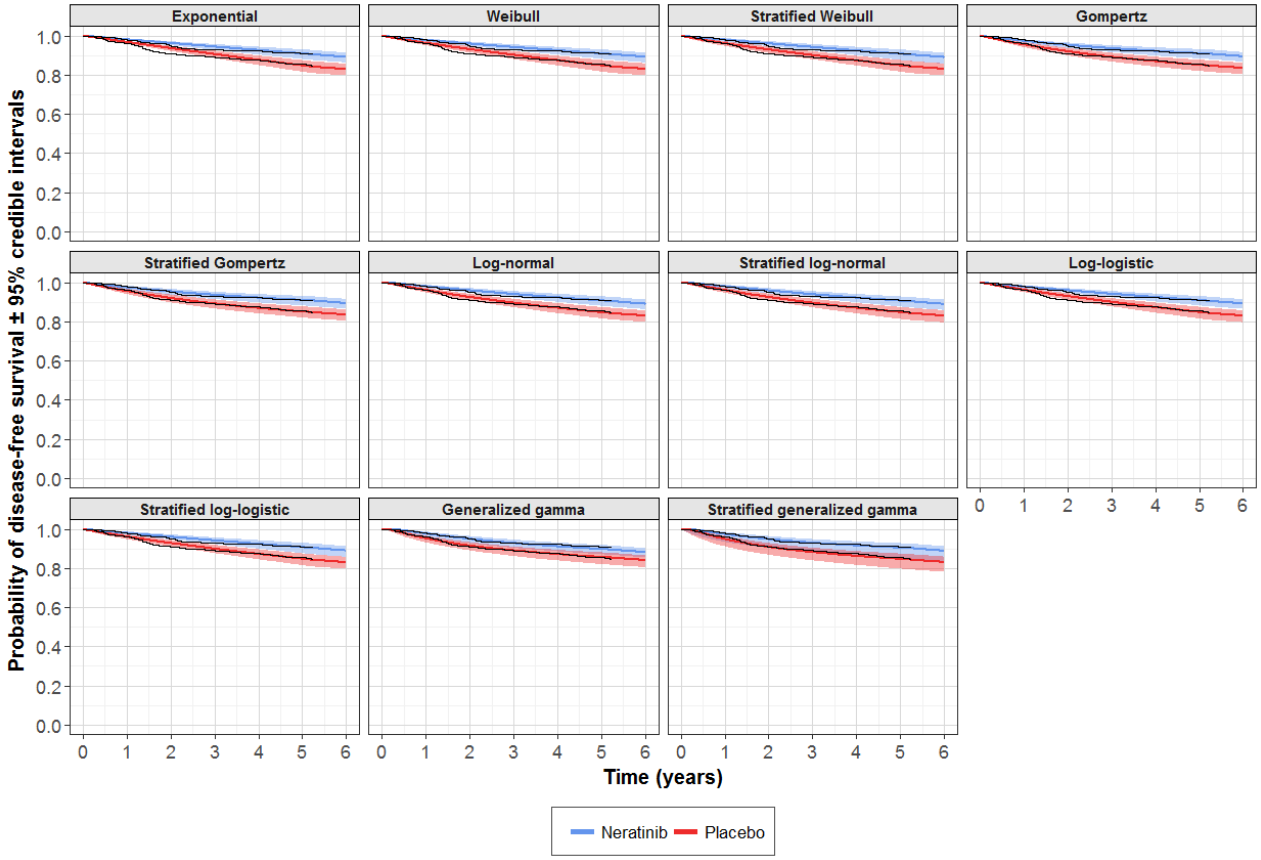
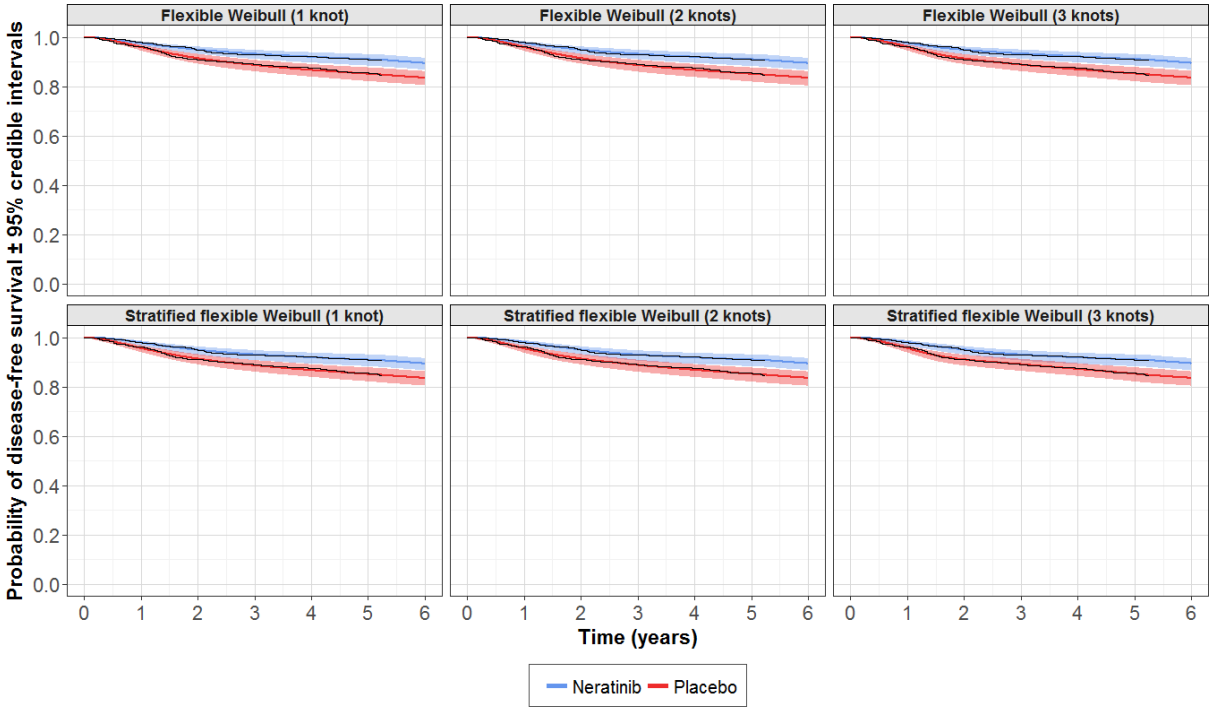


Figure 14 in Appendix L of the CS[21]
CS = company submission; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive

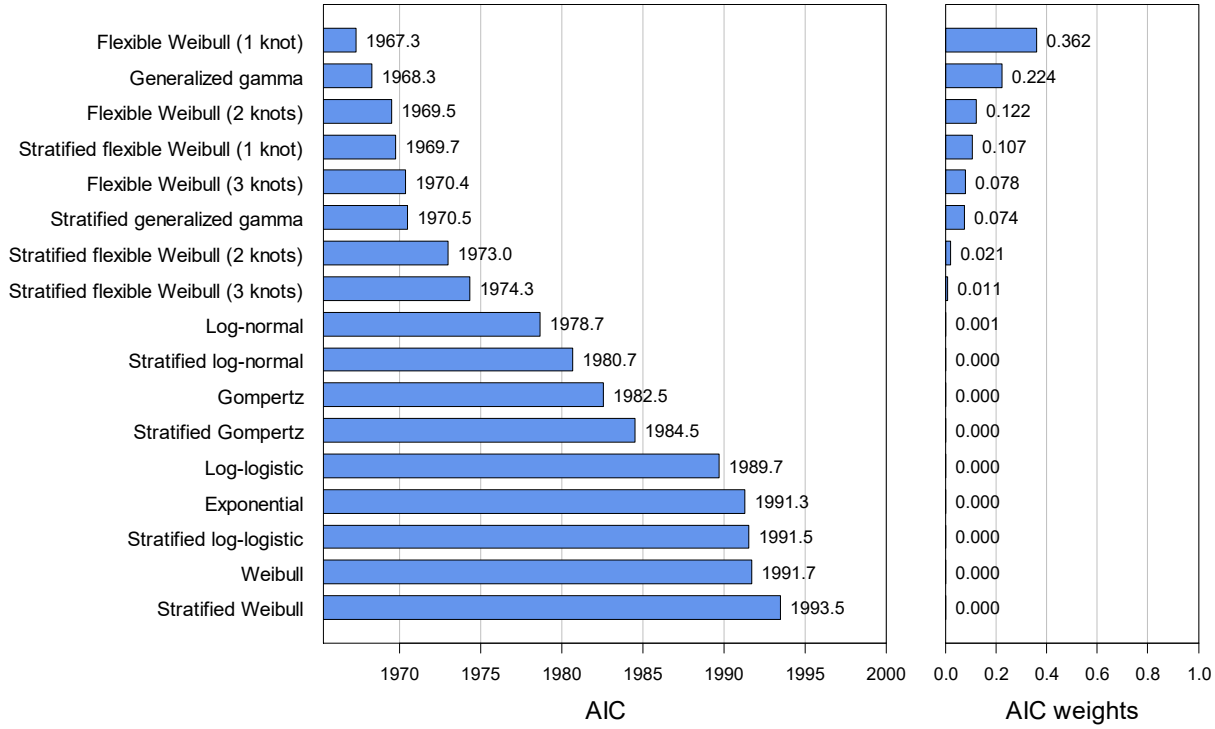
Figure 5.9: Flexible spline–based Weibull models fitted to the ExteNET trial data: disease-free survival: trastuzumab therapy completed within the past 12 months: HR+



Based on Figure 15 in Appendix L of the CS[21]
CS = company submission; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive

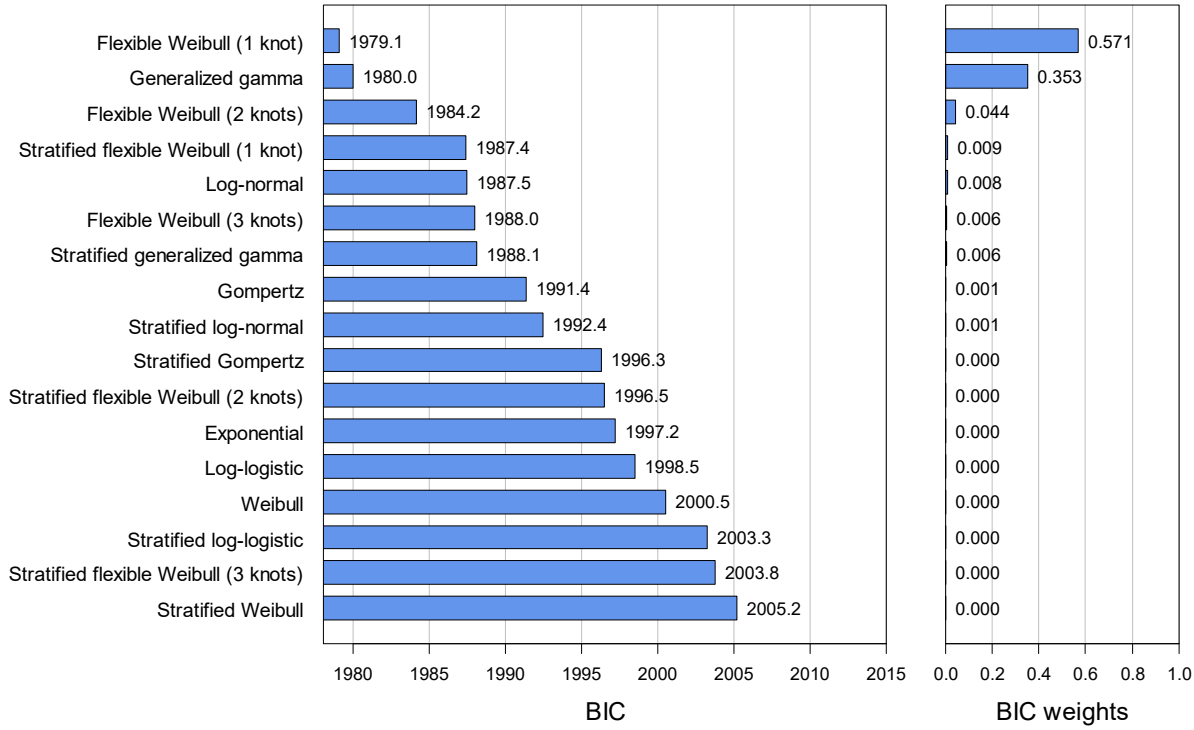
After the visual inspection of the KM curves, the company presented the AIC, BIC and IBS goodness-of-fit statistics for all the parametric models included in the submission. These can be seen in Figures 5.10 to 5.12, respectively. Based on these statistics, the generalised gamma and (some of the) flexible spline–based Weibull models provided the best fit, although for IBS there were other models (e.g. Gompertz, stratified Gompertz, stratified log-normal, etc.) with the same score.

Figure 5.10: AIC and Akaike weights for models fitted to the disease-free survival data from the ExteNET trial data: trastuzumab therapy completed within the past 12 months: HR+



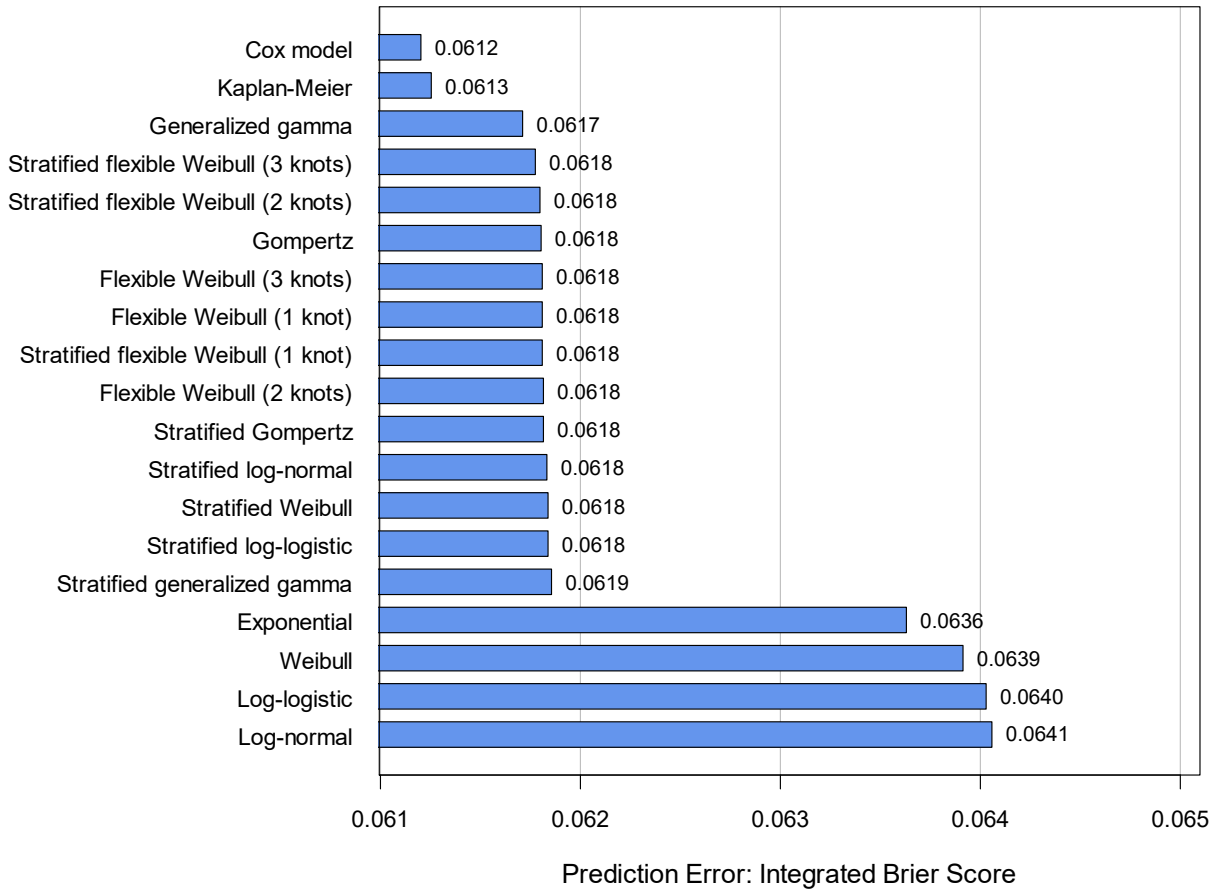
Based on Figure 16 in Appendix L of the CS[21]
AIC weights indicates the probability of best model
AIC = Akaike information criterion; CS = company submission; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive

Figure 5.11: BIC and weights for models fitted to the disease-free survival data from the ExteNET trial data: trastuzumab therapy completed within the past 12 months: HR+



Based on Figure 17 in Appendix L of the CS[21]
BIC weights indicate the probability of best model
BIC = Bayesian information criterion; CS = company submission; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive

Figure 5.12: IBS for the models fitted to disease-free survival from the ExteNET trial data: trastuzumab therapy completed within the past 12 months: HR+



Based on Figure 19 in Appendix L of the CS[21]
CS = company submission; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive; IBS = Integrated Brier score

Based on the above information (visual assessment of the KM and survival parametric curves and goodness-of-fit statistics), the conclusion in Appendix L was the following: "*the models that gave the best visual fit, AIC, BIC and IBS statistics were the generalised gamma and spline-based Weibull models. However, the generalised gamma appeared to give a poor fit at the end of the trial follow-up. Both stratified and non-stratified models performed well. The bootstrap cross-validation showed that there was some uncertainty in the choice of model, with models such as Gompertz also performing well*".[21] The company chose the flexible Weibull (with one knot) for the base-case and the Gompertz for scenario analysis.

The ERG does not completely agree with the aforementioned conclusion. While the methods used to assess goodness-of-fit are correct, the way the company chose the parametric distributions seems arbitrary, especially when it comes to the Gompertz distribution. Based on the AIC, it seems reasonable to choose the flexible Weibull (with one knot) as potential candidate since it has the lowest AIC. However, between this distribution and the Gompertz there are nine distributions with an AIC lower than the Gompertz AIC. Therefore, based on the AIC, it is unclear why the Gompertz has been chosen as candidate and not some of the other distributions. The same could be said about the BIC. Based on BIC values, the flexible Weibull (with one knot) is again giving the lowest BIC, so it is a good candidate, but there are six distributions between this one and the Gompertz. Regarding IBS, the company mentioned that, "*out of the parametric models, the generalised gamma and flexible spline–*

based models gave the most reliable predictions over the timeframe of the trial". However, looking at the values in Figure 5.12, this is not completely true since there are 11 distributions in total with the same score: six of them are flexible spline models but the other five are not.

In the ERG's opinion, stratified models should have also been explored since, as explained in the previous section, it is not completely clear that the proportional hazards assumption holds. Besides that, the ERG considers that other information could have been used to help choosing candidates for modelling iDFS. For example, the shape of the hazard rates in Figure 5.4 (decreasing in time) and the shape of the hazard ratio in Figure 5.5 (increasing in time in a concave fashion) could have been used for this purpose. The hazard rate functions for the parametric distributions included in the economic model are shown in Appendix 3 (see Figure A3.1). From this figure it can be seen that the Gompertz, stratified Gompertz, Weibull, stratified Weibull, log-logistic and stratified log-logistic distributions resulted in decreasing hazard rate functions and, therefore, they might be considered as good candidates to model iDFS in the economic model, if it is assumed that the shape of the hazard rate functions should resemble the curves observed in Figure 5.4. Similarly, Figure A3.2 in Appendix 3 shows the hazard ratios for the parametric distributions included in the economic model. From this figure it can be seen that the stratified Weibull, lognormal, stratified lognormal, stratified log-logistic, generalised Gamma, stratified generalised Gamma and the stratified flexible Weibull (with one knot) distributions resulted in concave-increasing hazard ratios and, therefore, they might be considered as good candidates to model iDFS in the economic model if it is assumed that the shape of the hazard ratio should resemble the curve shown in Figure 5.5.

However, it should be acknowledged that there is also uncertainty regarding this assessment of the hazard rate functions and the hazard ratio. In Appendix L of the CS, it was mentioned that "*different approaches to smoothing the hazard rates may produce different conclusions*".[21] For that reason, in the clarification letter (question B10c), the ERG asked the company to explore different approaches to smoothing the hazard rates and compare their conclusions.[41] Unfortunately, the company did not provide such analyses because "*smoothing of the hazard rates was not used in the survival analysis*".[16] One of the purposes of clarification question B10c was to explore whether the shape of the hazard rates presented in Figure 5.4 could be attributed to the method used for smoothing them or not. Hazard rates based on observed data are not necessarily smooth functions. Different approaches to smooth them, may result in different shapes of the hazard rates.[44] The one provided by the company in Figure 5.4 is, therefore, one possible shape but different shapes might also be possible. The ERG considers that there is uncertainty regarding the shapes of the hazard rates (and the hazard ratio based on such hazard rates). Thus, parametric distributions whose hazard rates are different from the ones in Figure 5.4 should not be excluded as potential candidates to model iDFS, if these parametric distributions perform well according to the other methods considered by the company (visual inspection of the KM curves and goodness-of-fit statistics).

Furthermore, it should also be emphasised that the shape of a hazard rate function has an underlying clinical meaning. For the base-case analysis, the company chose a flexible-spline Weibull (with one knot) to model iDFS, and a Gompertz distribution in scenario analyses. The hazard rate functions based on these two distributions can be seen in Figure 5.7. It is clear that the shapes are different and so is the clinical interpretation. The hazard rate function for the flexible Weibull distribution starts at zero and increases for approximately one year. Therefore, by choosing that distribution, it is implicitly assumed that the risk of experiencing an iDFS event is continuously increasing for about one year, after which the risk starts to decline. However, if a Gompertz distribution is chosen to model iDFS, it is implicitly assumed that the risk of experiencing an iDFS event declines right from the start. The plausibility of the shape of the hazard rate function and its underlying clinical interpretation can be

used to select parametric functions. Such plausibility should be contrasted with trial data or confirmed by clinical experts. With the smoothed hazard rates provided in Figure 5.4, it would seem more appropriate to assume that the hazard rates will not increase in the beginning. Nonetheless, as mentioned above, this is uncertain, and it might be simply due to the method used to smooth the curves. Unfortunately, the company did not address this issue in the submission nor in the response to the clarification letter. Since some of the parametric distributions giving the best fit are those whose hazard rate functions increase in the beginning, the ERG considers appropriate to include these distributions as potential candidates to model iDFS.

Finally, the ERG conducted an overall goodness-of-fit assessment based on all the information presented by the company (visual fit to KM, hazard rate and hazard ratio curves, and AIC, BIC and IBS goodness-of-fit statistics) either in the main submission document or in the appendices. A summary is presented in Table 5.3. The following assumptions were made by the ERG while assessing the goodness-of-fit of the parametric distributions:

- All six methods used to assess goodness-of-fit (visual fit to KM curves, shape of hazard rate and hazard ratio curves, and AIC, BIC and IBS goodness-of-fit statistics) were considered equally important.
- Visual fit with KM curves was based on the company's assessment. The ERG is more neutral regarding this assessment.
- Based on Burnham and Anderson rule of thumb,[45] it was considered that a difference in AIC less than 4 with respect to the AIC for the flexible Weibull (the one with the lowest AIC) was appropriate, between 4 and 7 was neutral, and larger than 10 was inappropriate.
- Based on Raftery rule of thumb,[46] it was considered that a difference in BIC larger than 10 with respect to the BIC for the flexible Weibull (the one with the lowest BIC) was inappropriate.
- The ERG is not aware of any rule of thumb for IBS. Therefore, all distributions with and IBS similar to the generalised Gamma were considered appropriate.
- Distributions with hazard rates declining from the beginning were considered appropriate; distributions with increasing hazard rates at the start and declining before 12 months (as in the flexible Weibull [with one knot]) were considered neutral; the remaining distributions were considered inappropriate.
- Distributions with an increasing concave hazard ratio were considered appropriate; distributions with increasing non-concave hazard ratio were considered neutral; the remaining distributions were considered inappropriate.

Based on the assessment summarised in Table 5.3, the ERG considered that the best candidate distributions to model iDFS were (by order of preference) the stratified generalised Gamma, stratified flexible Weibull (with one knot), flexible Weibull (with one knot), flexible Weibull (with two knots) and generalised Gamma. The ERG acknowledges that the method used to choose parametric distributions is one of many possible but it overcomes the main limitation with the company's approach, where part of the results provided within the submission were ignored, resulting thus in a biased assessment.

Table 5.3: Overall goodness-of-fit assessment by the ERG

Parametric model	Visual fit with KM	AIC	BIC	IBS	Visual hazard rates	Visual hazard ratio	Overall assessment [score]
Exponential	😐	☹	☹	☹	☹	☹	☹ [1.17]
Weibull	😐	☹	☹	☹	☺	☹	☹ [1.50]
Stratified Weibull	😐	☹	☹	☺	☺	☺	😐 [2.17]
Gompertz	☺	☹	☹	☺	☺	☹	😐 [2.00]
Stratified Gompertz	😐	☹	☹	☺	☺	☹	☹ [1.83]
Lognormal	😐	☹	☺	☹	😐	☺	😐 [2.00]
Stratified Lognormal	😐	☹	☹	☺	😐	☺	😐 [2.00]
Log-logistic	😐	☹	☹	☹	☺	😐	☹ [1.67]
Stratified log-logistic	😐	☹	☹	☺	☺	😐	😐 [2.00]
Generalised Gamma	☹	☺	☺	☺	😐	☺	☺ [2.50]
Stratified generalised Gamma	☺	☺	☺	☺	😐	☺	☺ [2.83]
Flexible Weibull (1 knot)	☺	☺	☺	☺	😐	☹	☺ [2.50]
Flexible Weibull (2 knots)	☺	☺	☺	☺	😐	☹	☺ [2.50]
Flexible Weibull (3 knots)	☺	☺	☺	☺	☹	☹	😐 [2.33]
Stratified flexible Weibull (1 knot)	☺	☺	☺	☺	☹	☺	☺ [2.67]
Stratified flexible Weibull (2 knots)	☺	😐	☹	☺	☹	☹	☹ [1.83]
Stratified flexible Weibull (3 knots)	☺	😐	☹	☺	☹	☹	☹ [1.83]

Visual fit with KM: Based on company's assessment. The ERG is more neutral regarding this assessment.
AIC: Define $\Delta i = AICi - AICmin$, where AICi is the AIC of the i-th model, and AICmin is the lowest AIC, obtained for Flexible Weibull (1 knot): ☺ = $\Delta i < 4$; 😐 = $4 < \Delta i < 7$; ☹ = $\Delta i > 10$.
BIC: Define $\Delta i = BICi - BICmin$, where BICi is the BIC of the i-th model, and BICmin is the lowest AIC, obtained for Flexible Weibull (1 knot): ☺ = $\Delta i < 10$; ☹ = $\Delta i > 10$.
IBS: Could not find any rule of thumb. ☺ = similar to Generalised Gamma.
Hazard rates: ☺ = declining from the beginning; 😐 = decline starts before flexible Weibull (1 knot) [both arms at month 12]; ☹ = none of the previous two.
Hazard ratio: ☺ = increasing concave function; 😐 = increasing non-concave function; ☹ = non-increasing function.
Overall score: average from ☺ = 3 points; 😐 = 2 points; ☹ = 1 point.
AIC = Akaike information criterion; BIC = Bayesian information criterion; ERG = Evidence Review Group; IBS = Integrated Brier score; KM = Kaplan-Meier

Duration and type of treatment effect

The iDFS hazard rates based on the five-year follow-up data from the ExteNET HR+ population shown in Figure 5.4, suggest a treatment effect longer than four years after one year of treatment with neratinib (HR = 0.58, observed four years after one year of treatment with neratinib). The next step is then to estimate the time for which the treatment effect would last in reality and to apply this in the economic model. To do so, the company extrapolated (linearly) the hazard ratio (obtained from the hazard rates in Figure 5.5 – so for the HR+ population) to identify the time point at which the hazard ratio would become one, which indicates the moment where the treatment effect disappears. As shown in Figure 5.5, this would not happen at any time point within the modelled time horizon. As mentioned in the previous sub-section, at a certain time cycle, patients in the model "switch" from the ExteNET iDFS hazard rate to the general population (mortality) hazard rate when the two hazard rates cross (so that it is assumed that the ExteNET hazard rate cannot be lower than the general population hazard rate). The switching point determines the maximum duration of the treatment effect and depends on the parametric curves chosen to model iDFS in ExteNET and to model mortality in the general population. In the company's base-case, this "switching" to the general population mortality occurs at year 10.75 (month 129) in the neratinib arm and at year 14.6 (month 176) in the placebo arm.[2] Beyond the point where placebo and general population mortality hazards are the same, a treatment effect is implicitly no longer applied, since for both treatment arms the iDFS hazard rate is modelled according to the general population mortality.

Based on the assessment of proportional hazards conducted by the company (discussed in the beginning of this section 5.2.6.1), in the base-case analysis, the company applied the same hazard ratio observed at the end of the follow-up period (HR = 0.58) beyond the trial time horizon. This means that in the model the treatment effect is maintained from year 5 until year 10.75 (month 129 – when patients' hazards in the neratinib arm follow those from the general population mortality). What happens in the base-case is that the HR equal to 0.58 is applied from month 62 to month 129 (thus, for 5.58 years in total). Then, from month 130 to month 176 (during 3.83 years), the HR increases (on average 0.009 per year) until it becomes one. So implicitly, there is a waning of the treatment effect starting at month 130. In total, 14.6 years of neratinib treatment effect are assumed for the base-case (starting from baseline until the time point where placebo and general population mortality hazards are the same).

In an additional scenario, a more rapid waning of treatment effect was explored by the company. In particular, it was assumed a tapering of the treatment effect over a period of 8.65 years after the end of the trial (from month 63 to month 166). This period was estimated based on a linear extrapolation of the hazard ratio observed in ExteNET for patients regardless of HR status. The plot (not shown here) is similar to that in Figure 5.7 but in this case the extrapolation of the hazard ratio reaches one after 13.9 years (see Figure 12.B in Appendix L of the CS).[21] In this scenario, the "switching" to the general population mortality hazard occurs at month 176 in both arms. An increasing HR (starting at 0.58 and increasing by 0.004 per year) is applied from month 63 to month 166 (for 8.58 years). Then, from month 166 to month 176 the hazard ratio is equal to one but both arms are modelled following

[2] In the company submission, the "switching" points mentioned by the company are year 12 in the neratinib arm and year 16 in the placebo arm. These values do not match with those in the electronic model dated 19 March 2019, which are the ones mentioned in this report.

placebo hazards. From month 176 the hazard ratio is still one but both arms are modelled following general population mortality hazards. Thus, there is a waning of the treatment effect starting at month 63 until month 166. In total, 13.83 years of neratinib treatment effect (starting from baseline) are assumed for this scenario.

ERG comment: With the evidence presented by the company, it seems reasonable to assume that the duration of the neratinib treatment effect is longer than five years (starting form baseline) and up to a maximum of 14.6 years (corresponding to the time point where placebo and general population mortality hazards are the same) in the base-case. There remains the question whether the duration of the neratinib treatment effect is shorter than those 14.6 years. The impact on the ICER of different durations for the neratinib treatment effect can be seen in section 7 of this report.

Regarding the type of treatment effect (i.e. constant or tapered), the company concluded that "g*iven the continued treatment effect shown during the trial and the lack of evidence of the treatment effect waning considerably towards the end of the trial, base-case analyses were based on the extrapolation of data from ExteNET without further adjustments of treatment effect beyond the trial time horizon*".[1] The ERG does not completely agree with this conclusion for the reasons explained in the previous sub-sections. In particular, stating that there is "*lack of evidence of the treatment effect waning considerably towards the end of the trial*" seems a rather subjective interpretation of the evidence presented and results from the company ignoring part of the results provided within the submission. The analysis of the hazard rates and the hazard ratio in Figures 5.4 and 5.5 clearly indicates a waning of the treatment effect.

There is also uncertainty regarding the "switching" point from iDFS to general population mortality since this point is determined by the choices made when selecting iDFS and general population mortality curves. The company highlighted the limited evidence available regarding this issue and sought clinical input that confirmed that the plausibility of assuming that the iDFS risk would approach that of the general population at some point, although it is uncertain to determine exactly at what point in time. In TA569, it was assumed that the risk of an iDFS event at the end of the HERA trial was similar to that of the UK general population. The clinical input sought by the company of this appraisal, indicated that this was uncertain. The company explored this issue further and observed that the hazard rate at the end of the HERA trial (equal to 8.5 years [102 months] after initiation of neratinib treatment) were higher for the HERA population compared with that of the general population. Using a Gompertz and a flexible Weibull (with two knots) distribution to model DFS in HERA (the models with the best fit to the digitised DFS HERA data),[21] and a flexible Weibull (with two knots) distribution for the general population mortality, the company analyses provided a time span between 125 to 175 months (so between 10.4 and 14.6 years) after initiation of neratinib treatment, where the risk of an iDFS event is likely to be equal to that of the general population. Based on this, the company concluded that "*it seems plausible to assume an increase iDFS risk compared with the general population for a longer time period than the 10 years after initial breast cancer diagnosis cited in the ongoing NICE appraisal of pertuzumab (TA569)*".[1] The ERG agrees with this statement but, in light of the acknowledged uncertainty, the opposite might also be plausible.

5.2.6.2 Recurrence

The company estimated the proportion of patients transitioning from iDFS to local or distant recurrence based on the events observed in the ExteNET trial after five years. The observed proportions for each arm, as included in the base-case analysis, are shown in Table 5.4.

Table 5.4: Type of iDFS event observed in the ExteNET trial (five-year data)

	Neratinib (n=670)	Placebo (n=664)
Patients with events, n (%)	51 (7.6)	89 (13.4)
Local/regional invasive recurrence (%)	5 (0.7)	18 (2.7)
Invasive ipsilateral breast tumour recurrence (%)	2 (0.3)	5 (0.8)
Invasive contralateral breast cancer (%)	2 (0.3)	5 (0.8)
Distant recurrence (%)	40 (6.0)	63 (9.5)
Death from any cause (%)	2 (0.3)	3 (0.5)
Patients censored, n (%)	619 (92.4)	575 (86.6)
Proportion distant recurrence, n (%)	40/49 (81.6)	63/91 (69.2)
Proportion other recurrences, n (%)	9/49 (18.4)	28/91 (30.8)

Based on Table 31 of the CS[1]
CS = company submission; iDFS = invasive disease-free survival.

Local recurrence

To model local recurrence the company took the approach followed in the NICE appraisal of pertuzumab (TA569).[25] Therefore, it was assumed that patients experiencing a local recurrence would stay in the local recurrence health state for one year, in which they receive additional adjuvant therapy. After that, they either transition to the remission health state or die (due to all-cause mortality). In the remission health state, patients can either die from all-cause mortality or experience another recurrence, which in line with NICE appraisal TA569, it is assumed to be distant. The company assumed a constant monthly transition probability from remission to distant recurrence (0.00757). This value was used in TA569,[25] and was obtained from a study by Hamilton et al. 2015.[47]

ERG comment: In line with TA569,[25] the company assumed that patients experiencing a local recurrence would stay in the local recurrence health state for one year. The company acknowledged that this might not be completely realistic, since, in reality, patients may experience metastases during this year. Nevertheless, it was considered as a reasonable assumption by the company and it was used in the base-case analysis. The impact of this assumption on the model results was explored in scenario analyses. The ERG agrees with this approach.

In the clarification question B17a, the ERG asked the company to justify the constant value used for the transition probability from remission to distant recurrence.[41] The company indicated that transitions from remission to distant recurrence were not followed in the ExteNET trial.[16] Therefore, an external source for that probability had to be sought. However, the company did report that, in total, [redacted] within five years follow-up. Based on this, the company considered that it was appropriate to use the probability form TA569 in the base-case analysis. Since there were no other available data, in section 7.2 of this report, the ERG explored the impact of this probability on the model results.

Distant recurrence

The blinded post-distant recurrence survival (PDRS) data from both arms of the ExteNET trial were used by the company to model mortality from distant recurrence, where parametric survival models were fitted to the label population data in order to extrapolate survival beyond the observed follow-up

time. The company also explored the impact of TTDR on PDRS as observed in ExteNET, since these two measures have been shown to be correlated.[48, 49] These analyses suggested that patients with a recurrence within the first year since randomisation have a poorer survival than patients with a later recurrence. The two PDRS KM curves selected by the company are shown in Figure 5.13. In the base-case analysis, two parametric curves were fit to these KM curves.

Figure 5.13: ExteNET: Kaplan-Meier plot of analysis of overall survival post distant recurrence for HR+ patients who completed trastuzumab ≤ 1 year and had distant recurrence ≤ 12 months vs. > 12 months from randomisation, ITT population

Based on Figure 36 of the CS[1]
CS = company submission; HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive; ITT = intention-to-treat

The process for fitting survival models to patient-level data was as explained in section 5.2.6.1 of this report for iDFS. Based on AIC and BIC values, provided in Table 34 and 35 of the CS (not shown here),[1] the company chose the exponential and Gompertz distributions as the best candidates. Visual inspection of Figure 5.14, led the company to choose the Gompertz as the base-case distribution.

Figure 5.14: ExteNET: plot of survival curves for overall survival post-distant recurrence > 12 months and ≤ 12 months from randomisation compared with ExteNET Kaplan-Meier curves

Based on Figure 38 of the CS[1]
CS = company submission

ERG comment: Based on the information presented by the company (visual assessment of the KM and survival parametric curves, AIC and BIC goodness-of-fit statistics), the ERG agrees with the choices made by the company for the base-case. However, it should be noted that the visual fit looks poor in general and it is difficult to decide, based on Figure 5.14, whether the Gompertz distribution provides a better fit than the exponential. Seeing the AIC and BIC values, probably the Gamma and the Weibull distributions could have been used as well, although no plot to assess the visual fit to KM curves was provided by the company. The ERG explored this in section 7.2 of this report.

5.2.6.3 General population mortality

The company assumed that, in the economic model, death due to breast cancer is only possible from the distant recurrence health state. For all the other health states, mortality risk was modelled according to age-adjusted survival probabilities for the female general population.[50] The company based this assumption on the low number of deaths from any cause as an iDFS event observed in ExteNET (2 [0.3%] in the neratinib arm and 3 [0.5%] in the placebo arm). The same assumption was considered in TA569.[25]

General population mortality data were taken from UK lifetables.[50] Based on these data, the company "reconstructed" 10,000 patients. This number was chosen by the company as it kept the running time at a reasonable level while being able to capture the shape of the survival curve. Subsequently, parametric survival models were fitted to these patient-level data. Predictions were also made from the distribution of the mean age in the trial. The company deemed this approach (fitting parametric

curves to reconstructed patient-level data instead of using the lifetables directly) necessary in order to integrate the external evidence for iDFS (from the HERA trial) into the iDFS extrapolations, which was used in scenario analyses, and to make predictions based on the cycle length of the model (one month) instead of one year.

The process for fitting parametric survival models to the "reconstructed" patient-level data was as explained in section 5.2.6.1 of this report for iDFS. Based on visual assessment of the KM and survival parametric curves, AIC and BIC goodness-of-fit statistics provided in Appendix L.6.2 of the CS,[21] the company chose a flexible spline–based Weibull model with two knots to model general population mortality.

ERG comment: Based on the information presented by the company (visual assessment of the KM and survival parametric curves, AIC and BIC goodness-of-fit statistics) in Appendix L.6.2 of the CS,[21] the choice of a flexible spline–based Weibull model with two knots to model general population mortality, seems appropriate to the ERG. Since the data used were taken from UK lifetables, it is expected that little uncertainty is associated to this parameter. Therefore, it is not necessary to explore this in additional scenarios. However, the ERG would question the assumption that the mortality of those in the states of iDFS, local recurrence and remission is that of the general population, particularly given the absence of treatment-specific OS data.

5.2.7 Adverse events

Data regarding the incidence and mean number of events for those AEs experienced by at least 1% of patients were included in the model and taken from the label population of the ExteNET trial. The exception to this was the incidence and mean number of events of diarrhoea with prophylaxis, which were taken from the CONTROL trial safety population who were mandated loperamide alongside neratinib. The majority of AEs observed were diarrhoea events in the neratinib group, which the company state is expected from an EGFR-targeted agent. All other included AEs occurred in fewer than 4% of patients. Table 5.5 shows the incidence and mean number of events inputted into the model. Utility decrements (section 5.2.8.3) and costs (section 5.2.9.3) associated with AEs were then estimated per AE episode and applied once at the beginning of the simulation based on the proportion of patients in each treatment arm experiencing AEs.

Table 5.5: AE-related input parameters

Adverse event	Incidence (%)		Events (mean)		Source
	Neratinib	Placebo	Neratinib	Placebo	
Diarrhoea AEs					
Diarrhoea grade 1/2 with prophylaxis	47.5%		3.5		CONTROL safety population loperamide group
Diarrhoea grade 1/2 without prophylaxis	55.1%	32.4%	14.6	5.2	ExteNET label population
Diarrhoea grade 3/4 with prophylaxis	30.7%		1.6		CONTROL safety population loperamide group
Diarrhoea grade 3/4 without prophylaxis	39.4%	1.1%	2.7	1.3	ExteNET label population
Non-Diarrhoea grade 3/4 AEs					
Vomiting	3.6%	0.3%	1.50	1.0	ExteNET label population
Nausea	1.4%	0.3%	1.00	1.0	

Adverse event	Incidence (%)		Events (mean)		Source
	Neratinib	Placebo	Neratinib	Placebo	
Abdominal pain	1.7%	0.2%	1.09	1.0	
Fatigue	2.0%	0.3%	1.15	1.5	
Alanine aminotransferase increased	1.2%	0.3%	1.00	1.0	
Based on Tables 37 and 38 in CS[1] AE = adverse event; CS = company submission					

ERG comment: The incidence and mean number of events of diarrhoea with prophylaxis using loperamide was obtained from the safety population of the CONTROL trial. This population does not match the ExteNET label population in terms of length of time from trastuzumab or HR status. The incidence and number of events of other AEs and of diarrhoea without prophylaxis pertain to the ExteNET label population. In their clarification response (question B27), the company stated that they did not have access to data from the CONTROL trial specific to the label population, however they did state that 73% of the CONTROL loperamide group matched the criteria for the label population.[16] The company also indicated that they were not aware of any clinical reason why the effect of diarrhoea prophylaxis would differ between the safety and label population.

5.2.8 Health-related quality of life

5.2.8.1 HRQoL data from clinical trials

In the ExteNET trial, HRQoL data were collected using the EQ-5D-3L at baseline and at month 1, 3, 6, 9, and 12 (end of treatment) for all patients on treatment (regardless of the treatment arm). Despite the stated main objective to estimate utility values for each of the health states in the model, no follow-up for HRQoL was conducted for patients discontinuing or experiencing recurrence except for 11 patients. Therefore, the HRQoL data collected were only used to estimate utility values for patients in the iDFS health state. The utility value for the remission health state was assumed to be equal to iDFS as in TA569.[25]

EuroQol 3 level (EQ-5D-3L) utility values were calculated based on the label iDFS population using the UK EQ-5D-3L value set,[51] and analysed using a generalised linear mixed model that included fixed effects for age, baseline utility and sequential/concurrent trastuzumab, and a marginal and a random effect for patient. Changes in utility over time, as well as changes in the impact of diarrhoea on utilities over time, were also explored by the company. Despite an indication of changes in utility over time, this was not included in the final model because it was not significant, and followed an unclear pattern. Due to unanticipated, as well as counterintuitive, results on the impact of different grades of diarrhoea, the utility values estimated for patients with diarrhoea were not used in the model.

ERG comment: The company stated in the submission that "*main objective of the utility analysis was to generate estimates of utility for each of the health states in the economic model*",[1] while only data from patients in the iDFS health state were considered for that analysis. This might be related to a protocol amendment that removed the requirement to collect HRQoL data. The result was a dataset on HRQoL that is incomplete and not fit for the purpose of the analysis (i.e. to obtain utility values for each health state in the model). The company also indicated that any estimates derived from this analysis should be interpreted with caution due to the presence of cases with missing values. Questionnaire completion rates were ≥ 85% from baseline to month 6 in both the neratinib and

placebo groups. Rates at later time points were lower in both groups (range, 69%-79%) because of a protocol amendment (October 2011) that removed the requirement for HRQoL data collection. Although the issue with missing values was mentioned in relation to unexpected and counterintuitive results on the impact of different grades of diarrhoea on HRQoL, the same model was used to estimate the utility value for iDFS. The mixed models used by the company can accommodate missing values but only under the assumption that data is missing at random can the results be considered unbiased. That assumption might be questionable here (e.g. patients who are worst off are the first to stop filling in the EQ-5D). However, this assumption is not testable and further analyses (e.g. using complete cases only) were not performed to check plausibility of the assumption. Therefore, similar concerns to those raised by the results for diarrhoea may also apply to the iDFS utility. This is important because the utility value used for the iDFS health state may have strong implications for the model results since, as can be seen in section 6.2.2 and section 7.2.1 of this report, the ICER is very sensitive to the value that is used for this parameter. For these reasons, the ERG has limited confidence in relying on the use of this utility value for iDFS to assess the cost effectiveness of neratinib.

The ERG requested the company (see clarification letter question B31),[41] to provide all the available utility data from ExteNET for the recurrence health states (available from 11 patients in the label population). From these patients, eight experienced distant recurrence and three local recurrence. Due to the small number of patients, the mixed-model analysis applied to iDFS, was not deemed appropriate by the company to analyse these data.[16] Instead, the company presented the following descriptive statistics for the utility values based on recurrence:

[redacted]

The company noted that, given the small sample size, there is a large degree of uncertainty associated with the above utility estimates, as indicated by the standard deviation and the range of values provided by the patients. The latter included [redacted].

5.2.8.2 HRQoL studies from the literature

A systematic literature review was conducted to identify studies reporting utility estimates in patients with HER2+ breast cancer, in combination with reviewing recent NICE submissions in similar indications. These strategies led to the identification of two studies: Lidgren et al. 2007 and Lloyd et al. 2006, both providing utility values for the model health states.[29, 30] In the company base-case, the utility value for local recurrence was taken from Lidgren et al. 2007, while the utility for distant recurrence was taken from Lloyd et al. 2006. In a scenario analysis, Lidgren et al. 2007 was used for the utility values of all health states with the purpose of removing potential effects of mixing data sources.

The company also considered utility decrements associated with adverse events. These were sourced from the literature and used in prior NICE appraisals (except for diarrhoea grade 1/2 which, according to the company, is rarely reported in NICE appraisals). The utility decrements associated with AEs were then combined with the proportion and duration of the AEs, as derived from the ExteNET or the CONTROL trial (in case of diarrhoea with prophylaxis), and were applied once at the beginning of the simulation.

ERG comment: The ERG also has concerns regarding the base-case utility value adopted from the Lloyd et al. 2006 study.[30] This study asked members of the UK general population to value vignettes,

which were developed for that study using expert opinion to reflect breast cancer health states. These health states were valued by general population participants using a standard gamble exercise. This study, therefore, did not measure and value health using the EQ-5D instrument as required by NICE. Furthermore, these measurements of health were not reported by patients. The Lidgren et al. 2007 study measured and valued the health of 361 breast cancer patients in Sweden using the EQ-5D-3L and the corresponding UK EQ-5D-3L value set.[29] Despite this study being conducted on patients outside of the UK, the ERG considers that this study better reflects the NICE reference case as valuation of health states were reported directly by patients, using the EQ-5D instrument and valued according to the UK value set.

5.2.8.3 HRQoL data used in the cost effectiveness analysis

Table 5.6 shows the utility values used in the model for all health states and for both base-case and scenario analyses.

Table 5.6: Health state utility values for base-case and scenario analysis

Health state	Base-case (source)	Scenario (source)
Disease free	0.837 (ExteNET)	0.779 (Lidgren et al. 2007)[29]
Local recurrence	0.696 (Lidgren et al. 2007)[29]	0.696 (Lidgren et al. 2007)[29]
Remission (assumed equal to disease free)	0.837 (Assumed as disease free)	0.779 (Lidgren et al. 2007)[29]
Distant recurrence < 12 months	0.521 (Lloyd et al. 2006)[30]	0.685 (Lidgren et al. 2007)[29]
Distant recurrence > 12 months	0.521 (Lloyd et al. 2006)[30]	0.685 (Lidgren et al. 2007)[29]
Based on Table 39 of the CS[1] CS = company submission		

Table 5.7 shows the utility decrements associated with AEs and the assumed mean duration (in weeks) of each AE.

Table 5.7: Utility decrements and mean duration of impact for adverse events

Adverse event	Utility decrement	Duration of impact (weeks)	
		Neratinib	Placebo
Diarrhoea grade 1/2	0.060 (Beusterien et al. 2009)[52]	14.6 without prophylaxis, 9.9 with prophylaxis	0.9
Diarrhoea grade 3/4	0.103 (Lloyd et al. 2006)[30]	1.2 without prophylaxis, 0.7 with prophylaxis	0.7
Vomiting	0.048 (Nafees et al. 2008)[53]	0.56	4.57
Nausea	0.048 (Nafees et al. 2008)[53]	1.13	4.29

Adverse event	Utility decrement	Duration of impact (weeks)	
		Neratinib	Placebo
Abdominal pain	0.048 (Assumption: same as nausea and vomiting)	1.83	0.14
Fatigue	0.115 (Lloyd et al. 2006)[30]	1.26	9.43
Alanine aminotransferase increased	0.048 (Assumption: same as nausea and vomiting)	1.2	9.64
Based on Table 40 of the CS[1] CS = company submission			

ERG comment: Based on the HRQoL evidence presented by the company, the ERG prefers a base-case analysis that makes use of the utility value for iDFS as derived from the ExteNET trial. Despite the limitations and concerns previously described in this section, this is still the only utility value directly sourced from the relevant population for this assessment. To reduce the possible impact of mixing data sources and to overcome the limitations of the utilities from the Lloyd et al. 2006 study previously described, for the remaining health states of the model, the ERG prefers the utility estimates from Lidgren et al. 2007. In section 7.2 of this report, the ERG explored the impact of using different utility values on the model results.

Finally, the company did not include age-related utility decrements in the model, despite reporting an indication of changes in utility over time. This decision was based on analysis results being non-significant and following an unclear pattern. The ERG would like to point out the misuse of p-values as in the assessment of proportional hazards in section 5.2.6.1.[40] Regarding the unclear pattern, it is difficult for the ERG to assess this, but it might simply be that ExteNET was not powered to detect differences in utilities over time. Since the overall utility of the general population is expected to decrease in time, the ERG considers it plausible to incorporate in the economic analysis the age-based decline in utilities from Janssen and Szende 2014.[54]

5.2.9 Resources and costs

5.2.9.1 Intervention costs and resource use

Intervention costs in the neratinib arm included the cost of drug acquisition, including prophylaxis and additional monitoring. Intervention costs in the placebo arm consist of endocrine therapy (also given as concomitant therapy in neratinib patients) with unit costs obtained from eMIT.

Neratinib is administered orally in 40 mg tablets and it is licenced according to a 240 mg (6 x 40 mg) dose, taken once daily continually for one year. The list price for a 180-tablet pack is [redacted], equivalent to [redacted] per 240 mg dose. The company stated that the actual mean neratinib treatment duration observed in the ExteNET label population, when discontinuation (due to adverse events, subject request, and protocol violations) was accounted for, was [redacted] months instead of the 12 months prescribed. The ExteNET trial also allowed dose reductions in response to adverse events. The relative actual dose intensity observed in the ExteNET label population was [redacted]% of planned 240 mg doses. Therefore, the aforementioned treatment duration and relative dose intensity are used in the model to calculate the total drug cost of neratinib.

Prophylaxis with loperamide was mandated in the CONTROL trial to prevent diarrhoea in the neratinib group. Unit costs for loperamide were taken from the eMIT database.[55] Treatment protocols from the CONTROL trial were used to estimate the cost of loperamide in the model. In CONTROL, loperamide was given to participants for a period of 28-56 days (1-2 cycles). The initial loperamide treatment protocol in CONTROL was a 4 mg initial dose, then 12 mg/day on days 1-3 and 6-8 mg/day on days 4-56, resulting in a total dose of 404 mg. Later this protocol was amended to a 4 mg initial dose followed up 12 mg/day on days 1-14, then 8 mg/day on days 15-56 resulting in a total dose of 500 mg. In the model base-case, loperamide was assumed to be provided for 56 days (two model cycles), at the higher total dose of 500 mg, which resulted in a total cost of £2.50 (for the two model cycles).

Additional monitoring costs were also assumed for patients taking neratinib, based on expert opinion from a panel of clinicians. The company reported that the SmPC stated that liver function should be monitored at 1 week, then monthly for the first three months and thereafter every six weeks while on neratinib treatment. Therefore, 10 liver function tests and 11 GP visits were assumed for neratinib patients in year 1 in the company base-case.

ERG comment: The ERG has concerns surrounding the calculation of treatment duration and relative actual dose intensity used in the model and the impact this had on the resulting estimate of treatment costs.

In the company submission, it is stated that in the CONTROL trial, where prophylaxis was mandated alongside neratinib, diarrhoea related dose holds and dose reductions were lower than in the ExteNET trial, where prophylaxis was not mandated (differences shown in Table 5.8). Therefore, the ERG considers that the value for relative actual dose intensity ([redacted]%) and resulting treatment cost incorporated into the company base-case are likely to be lower than would be observed in clinical practice, if prophylaxis with loperamide is expected. If prophylaxis for diarrhoea is to be assumed, then data from the CONTROL trial can be considered more relevant for dose reductions and hold due to diarrhoea. The percentage of patients experiencing dose hold and reductions related to diarrhoea in CONTROL was approximately half the percentage observed in ExteNET (see Table 5.8). Therefore, as mentioned above, it is likely that dose intensity will be higher in clinical practice (but not necessarily expected to be [redacted]%). Since the exact dose intensity is unknown, the ERG proposed reducing the doses lost ([redacted] - [redacted] = [redacted]) by half resulting in a dose intensity of [redacted]%. This was applied to the ERG preferred base-case in section 7.2 of this report.

The introduction of prophylaxis for diarrhoea may also be expected to reduce AE related discontinuations, although this is not observed in the comparison between the ExteNET and CONTROL discontinuation rates provided by the company (see Table 5.8), where the AE related withdrawals in CONTROL are higher (which seems to contradict the results regarding AE related dose reductions and holds). Because data from CONTROL did not support the ERG expectations regarding treatment discontinuation, in the ERG preferred base-case analysis, the ERG considered the same treatment duration as in the company's base-case ([redacted] months). The number of patients coming off the treatment before [redacted] months is likely to be underestimated since in the current analyses 100% of the patients are assumed to stay on treatment until [redacted] months. Therefore, treatment costs would be overestimated for those on treatment and the ICER would come down. However, the mean of [redacted] months might be an underestimate if all patients in clinical practice were to receive anti-diarrhoeal prophylaxis, as assumed in the base case. This is because it was estimated from ExteNET where anti-diarhhoea medication was only provided after the onset of symptoms and not as prophylaxis. It is impossible to know what the net effect on costs would be, but it is expected to be relatively small.

Table 5.8: Diarrhoea caused treatment discontinuation and dose hold and reduction rates across trials

	ExteNET safety population	CONTROL loperamide safety population
	Neratinib	Neratinib
Treatment discontinuation (%)	16.8	20.4
Dose reduction (%)	26.4	7.3
Dose hold (%)	33.9	15.3

Based on Table 25 of the CS[1]
CS = company submission

The tornado plot from the company base-case (see Figure 6.3) revealed that these two parameters have the largest impact on the ICER, increasing thus the importance that assumptions surrounding these parameters reflect clinical practice. Additional scenarios based on these two parameters were explored by the ERG in section 7.2 of this report.

Finally, as requested by the ERG in the clarification letter (question B22),[16] the company added to the model costs associated to concomitant and subsequent endocrine therapy alongside neratinib or standard care. This request was based on 98% of ExteNET patients receiving endocrine therapy. However, as shown in section 7.1.1 of this report, the inclusion of these costs in the model had a negligible impact on the results.

5.2.9.2 Health state unit costs and resource use

Resource use associated with breast cancer consisted of GP, oncologist social worker and clinical nurse specialist visits, district nurse home visits, mammograms and echocardiograms, multigated acquisition (MUGA) and computerised tomography (CT) scans. The company reviewed existing NICE appraisals in similar populations and sought expert opinion to estimate expected resource use specific to each health state in the model. In the base-case, assumptions regarding health state resource use were based on the NICE appraisal of pertuzumab (TA569) for adjuvant treatment of early HER2+ breast cancer.[25] Health state resource use and corresponding costs incorporated in the model are outlined in Tables 42 to 46 of the company submission.[1] Unit costs for the resources identified, outlined in Table 47 of the CS,[1] were obtained from NHS Improvement,[33] NICE clinical guidelines for familial breast cancer [34] and Curtis and Burns 2018.[32]

ERG comment: In the company base-case, health state resource use assumptions were based on the pertuzumab appraisal for adjuvant treatment of early HER2+ breast cancer.[25] However, it was unclear from the company submission how similar this patient population is to the neratinib label population and, therefore, how appropriate the assumptions made about health state resource use were. The company submission stated that expert opinion was also sought to "*validate resource use and costs included in the economic model*" (Appendix M of the CS).[21] However, no details were provided about whether any health state resource use assumptions, other than subsequent treatments following recurrence, were included in the discussion or any opinions were provided about the included health state resource use assumptions.

5.2.9.3 Adverse event costs

Adverse event costs were calculated as the sum product of the cost of each AE and the proportion of patients observed to experience that AE in the ExteNET label population. The exception was the incidence and number of events of diarrhoea with prophylaxis, which was estimated from the

subgroup of the CONTROL safety population who received mandated loperamide. This provided an average cost per patient, which was applied in the first cycle of the model. Only those AEs which occurred in at least 1.0% of ExteNET patients were included in the model. Adverse event costs were obtained from NHS Improvement[33] and inflated according to Curtis and Burns 2018.[32]

5.2.9.4 Subsequent treatment costs following recurrence

Follow up in the ExteNET trial did not include subsequent treatments received by patients following recurrence. Therefore, the company reviewed existing NICE appraisals in similar populations and sought expert opinion to inform the subsequent treatments which patients would be expected to receive following recurrence in clinical practice and the proportion of patients expected to receive each of the treatment options identified. In the company base-case, the subsequent treatments included and the proportion of patients assumed to receive them were taken from the NICE appraisal of pertuzumab (TA569) for adjuvant treatment of early HER2+ breast cancer.[25] Treatments were divided into those relevant for non-metastatic (local) recurrence, first-line early metastatic (distant) recurrence and second-line early metastatic (distant) recurrence. Costs of the drugs identified were taken from the eMIT and BNF databases.[55, 56] Drug doses were estimated according to the mean body surface area (1.80 m^2) and weight (72.64 kg) of patients from the ExteNET label population. Administration costs for identified subsequent treatments were taken from the NHS Reference Costs.[33] The company stated that the treatments identified and the proportions of patients assumed to receive, which were taken from the pertuzumab appraisal, were similar to the opinion of experts approached by the company. The treatments identified and their corresponding treatment shares adopted from the pertuzumab trial, as well as those estimated by expert opinion, are compared in Table 5.9.

Table 5.9: Subsequent treatments identified and estimated treatment shares – pertuzumab appraisal compared to clinical expert elicitation

Health state	Regimen	Treatment share	
		Pertuzumab appraisal[a]	Expert opinion[b]
Non-metastatic (local) recurrence	Trastuzumab IV + docetaxel	50%	50%
	Trastuzumab SC + docetaxel	50%	50%
First-line early metastatic (distant) breast cancer	Trastuzumab IV + docetaxel	23%	
	Pertuzumab + trastuzumab + docetaxel	71%	70%
	Docetaxel	6%	
	Trastuzumab emtansine		10%
	Trastuzumab IV/SC + weekly paclitaxel		10%
	Trastuzumab SC and endocrine therapy		10%
Second-line early metastatic (distant) breast cancer	Trastuzumab IV and capecitabine	6%	10%
	Trastuzumab SC and capecitabine	13%	
	Trastuzumab emtansine	76%	70%
	Lapatinib and capecitabine	6%	
	Trastuzumab		10%

Health state	Regimen	Treatment share	
		Pertuzumab appraisal[a]	Expert opinion[b]
	Capecitabine only		10%

[a] Based on Table 52 of the CS [1] [b] Based on Table 65 in Appendix M of the CS[21]
CS = company submission; IV = intravenous; SC = subcutaneous

ERG comment: Results of expert opinion regarding subsequent treatments that patients would be expected to receive following recurrence and the proportion of patients who would be expected to receive them were provided in Appendix M of the CS.[21] However, the company chose to adopt the subsequent treatments and treatment shares identified from the pertuzumab trial, stating that the values used were similar to those provided by expert opinion. Table 5.9, however, shows that the treatments identified and the expected treatment shares for distant recurrence differ somewhat between expert opinion and the pertuzumab appraisal. In their response to the clarification letter (question B23),[16] the company argued that the neratinib label population would be expected to follow the same subsequent clinical pathway as those who receive pertuzumab. The company also stated that, since expert opinion was provided by a single clinician, the values from the pertuzumab trial were more widely validated and justified. Unfortunately, the company declined to provide the results of an alternative scenario based on the values obtained from expert opinion. The ERG feels that little justification has been provided for the health state resource use assumptions made in the model. The tornado plot of the company base-case (see Figure 6.3) shows that the cost of the distant recurrence state parameter is found to have one of the largest impacts on the ICER. It is therefore particularly important that the costs of distant recurrence implemented are realistic for the label population.

6. Cost effectiveness results

6.1 Company's cost effectiveness results

The discounted base-case results indicated that, compared with placebo, neratinib generated [redacted] incremental QALYs, and [redacted] incremental LYGs, with (higher) incremental costs of [redacted]. Thus, the incremental cost effectiveness ratio (ICER) was £24,585 per QALY gained. The full (discounted) base-case results are presented in Table 6.1.

Table 6.1: Company base-case cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Neratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,585
Placebo	[redacted]	[redacted]	[redacted]				

Based on Table 55 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALYs = quality-adjusted life years.

The disaggregated discounted cost and QALY results by health state are given in Tables 6.2 and 6.3, respectively.

Table 6.2: Summary of costs disaggregated by health state

Health state	Costs intervention (Neratinib)	Costs comparator (Placebo)	Increment	Absolute increment	% absolute increment
Disease-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Local Recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distant Recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 53 in Appendix J of the CS[21]
[a] These are included in the disease-free health state, and are only displayed separately for informative purpose
CS = company submission

Table 6.3: Summary of QALYs disaggregated by health state

Health state	QALYs intervention (Neratinib)	QALY comparator (Placebo)	Increment	Absolute increment	% absolute increment
Disease-Free	14.58	13.40	1.17	1.17	76%
Local Recurrence	0.01	0.04	-0.03	0.03	2%
Remission	0.09	0.30	-0.21	0.21	14%
Distant Recurrence	0.15	0.29	-0.14	0.14	9%
Adverse events[a]	-0.042	-0.014	-0.028	0.028	1.82%
Total	14.83	14.03	0.80	1.55	100%

Based on Table 52 in Appendix J of the CS[21]

CS = company submission; QALY = quality-adjusted life year

Finally, the disaggregated discounted costs by category are given in Table 6.4.

Table 6.4: Summary of disaggregated costs by category

Cost category	Costs intervention (Neratinib)	Costs comparator (Placebo)	Increment	% increment
Study treatment (incl. drugs and diarrhoea prophylaxis)	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment (local and distant recurrence)	[redacted]	[redacted]	[redacted]	[redacted]
Health state costs (i.e. for monitoring and surveillance)	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (i.e. for additional monitoring of neratinib patients and adverse events)	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
Based on electronic model.				

6.2 Company's sensitivity analyses

6.2.1 Probabilistic sensitivity analysis

The company conducted probabilistic sensitivity analysis in which 5,000 iterations were run. The input parameters included in the PSA can be seen in Table 53 of the company submission.[1] The discounted results from the probabilistic model are shown below in Table 6.5. The incremental costs and incremental QALYs obtained from the probabilistic model were plotted in the cost effectiveness (CE) plane, from which a cost effectiveness acceptability curve (CEAC) was drawn. These are shown in Figures 6.1 and 6.2, respectively. The probabilistic ICER was £24,413 per QALY gained, compared to £24,585 per QALY gained in the deterministic model. The vast majority of the 5,000 iterations provided results in the north-east quadrant of the CE plane, where neratinib is both more costly and more effective than placebo. The CEAC showed that neratinib has a 36% probability of being cost effective at a threshold of £20,000 per QALY and a 60% probability of being cost effective at a threshold of £30,000 per QALY.

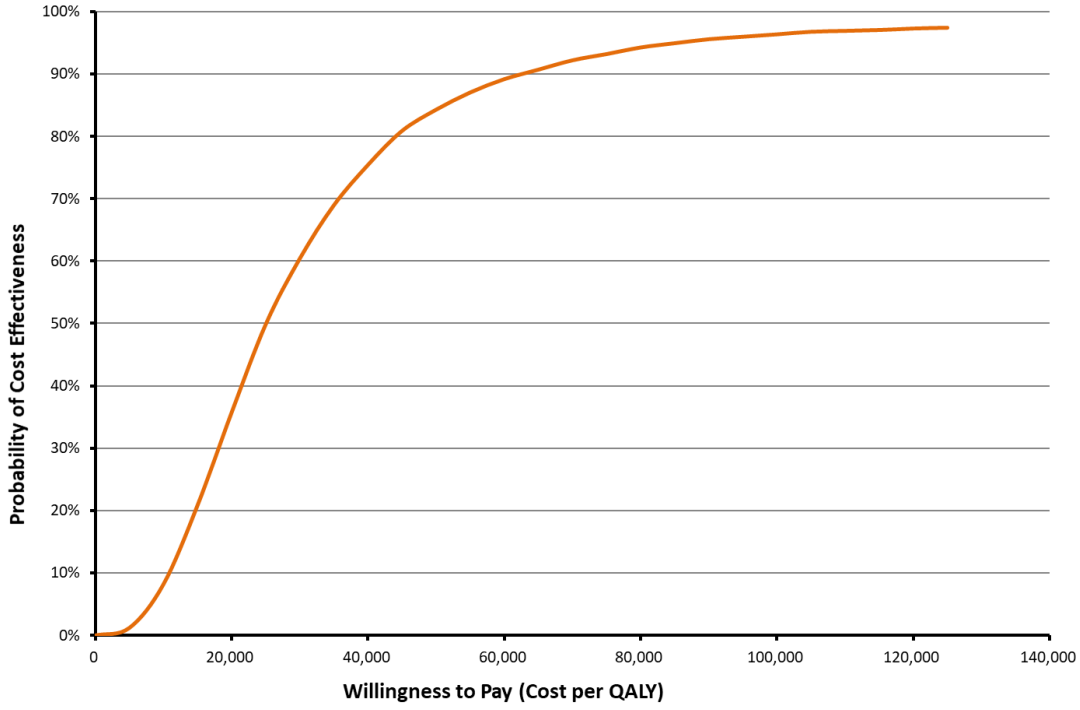
Table 6.5: Company base-case probabilistic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Placebo	[redacted]	[redacted]			
Neratinib	[redacted]	[redacted]	[redacted]	[redacted]	£24,413
Based on Table 56 of the CS[1] CS = company submission; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Figure 6.1: Scatterplot form the probabilistic sensitivity analysis iterations

Based on Figure 40 of the CS[1]
CS = company submission; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 6.2: Cost effectiveness acceptability curve



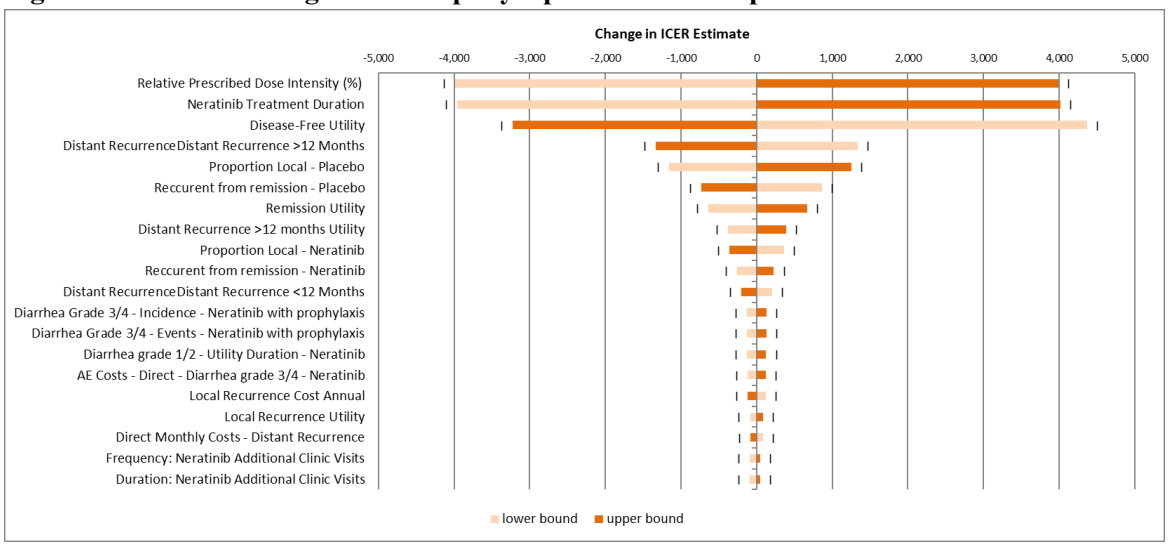
Based on Figure 39 of the CS[1]
CS = company submission; QALY = quality-adjusted life year

6.2.2 Deterministic sensitivity analysis

Seventy-nine parameters were included in the company's one-way deterministic sensitivity analysis. The value of each of these parameters was varied in turn by reducing and increasing the base-case

value by 10%, while keeping the remaining parameters constant at their base-case values. The tornado plot in Figure 6.3 displays the impact on the ICER of the 20 parameters which caused the largest fluctuations in the ICER. From the tornado diagram, it seems clear that the relative prescribed dose intensity of neratinib, the neratinib treatment duration and the assumed utility of the disease free (and remission) health state have the largest impact on the ICER.

Figure 6.3: Tornado diagram – company's preferred assumptions



Based on Figure 41 of the CS[1]
AE = adverse event; CS = company submission; ICER = incremental cost effectiveness ratio

ERG comment: The tornado diagram indicated that the dose intensity, treatment duration and iDFS utility are the most influential parameters. This might be the case, but the way the one-way sensitivity analysis (OWSA) was conducted, allowing 10% variation from mean value for all parameters, seems arbitrary and may not represent an equally plausible range of variation for all input parameters. Whenever possible, the limits of (95%) confidence intervals should be used for each parameter to calculate the upper and lower bounds of the bars in the tornado diagram. Given the time constraints associated with this project, the ERG was not able to correct this in the model. Therefore, the ERG considers that the tornado diagram presented above should be interpreted with caution.

6.2.3 Scenario analyses

The company undertook a series of eight scenario analyses in order to examine the impact of certain assumptions on the model outcomes. The results of the scenarios tested are summarised in Table 6.6. The scenario with the largest impact on the ICER was obtained by replacing the assumption of no treatment effect waning at the end of the trial (except for earlier crossover to general population mortality for neratinib arm) with the assumption that the treatment effect waned to no treatment effect 13.9 years post-randomisation. This caused the ICER to increase to £31,677. The scenario where a flexible-spline Weibull (with one knot) distribution was replaced by a Gompertz distribution to model iDFS increased the ICER to £30,190. The remaining scenarios resulted in ICERs values similar to the base-case ICER, indicating that the model is robust to changes in these assumptions.

ERG comment: All the scenario analyses conducted by the company resulted in quite moderate changes to the ICER. The largest difference with respect to the base-case ICER was observed in the scenario where a waning on the neratinib treatment effect (as opposed to a maintained effect after the trial follow-up period) was assumed. The ICER in this scenario was £31,677, thus, £7,092 larger than the base-case ICER. These results may lead to the erroneous conclusion that, in general, the ICER is

robust to most of the assumptions made in the model. As explained throughout section 5 of this report, the ERG identified several sources of uncertainty that seem to be relevant for the model results. However, most of them were only partially explored by the company (e.g. the selection of parametric curves to model iDFS) or simply not explored at all. Therefore, the ERG considers that the scenario analyses conducted by the company were insufficient to draw overall conclusions over the robustness of the model results. As explained in section 5.2.6.1, the company should have considered a wider range of distributions to model iDFS. Assumptions regarding the type and duration of the neratinib treatment effect, the source of utility data, the duration of neratinib treatment or the neratinib dose intensity should have been extensively explored, since these are expected to influence the model results. All these assumptions were tested by the ERG in section 7.2.2.

Table 6.6: Scenario analyses conducted by the company

Scenario	Alternative input	Base-case value	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base-case				[redacted]	[redacted]	24,585
1	Second-best-fitting distribution for ExteNET iDFS	Flexible-spline Weibull 1 knot	Gompertz	[redacted]	[redacted]	30,190
2	Second-best-fitting distribution for general population mortality	Flexible-spline Weibull 2 knot	Gompertz	[redacted]	[redacted]	24,793
3	Including HERA data in the extrapolation of iDFS	Using ExteNET and general population mortality	Using ExteNET, HERA, and general population mortality	[redacted]	[redacted]	24,912
4	Second-best-fitting distribution used for PDRS	Gompertz	Exponential	[redacted]	[redacted]	26,285
5	Waning of treatment effect	No treatment effect waning except for earlier crossover to general population mortality for neratinib arm	Waning to no treatment effect at 13.9 years from randomisation	[redacted]	[redacted]	31,677
6	Not stratifying PDRS by time of distant recurrence; < 12 months and ≥ 12 months	Separate survival incorporated for distant recurrence; < 12 months and ≥ 12 months	Same survival assumed regardless of time of distant recurrence	[redacted]	[redacted]	25,286
7	Proportion of local and distant recurrence	Treatment arm–specific proportion of local and distant	Average proportion of local and distant recurrence across	[redacted]	[redacted]	22,022

Scenario	Alternative input	Base-case value	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
		recurrence	both treatment arms			
8	Time in local recurrence before transitioning to remission	12 months	6 months	[redacted]	[redacted]	25,063

Based on Table 58 of the CS[1]
CS = company submission; HERA = HERceptin Adjuvant; ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; PDRS = post-distant recurrence survival; QALY = quality-adjusted life year

6.3 Model validation and face validity check

The following validation efforts were explicitly mentioned in the company submission:

1. Validation was performed by consulting external experts, including UK health economists with expertise in HTA, UK clinical oncologists, and a UK clinical expert with practical knowledge of treating patients with breast cancer. These consultations focused on model structure, the comparator and subsequent treatments, the validation of resource use and costs included in the economic model, and the modelling of overall survival, invasive disease-free survival, and duration of treatment effect.
2. Since no other data with a sufficient duration of follow-up are available on patients treated with neratinib, an external validation of the extrapolations for the intervention arm of the ExteNET trial could not be performed.
3. For the placebo arm of the ExteNET trial, external validation was performed using data from the HERA trial. Extrapolations for the ExteNET data were in line with those using data from the HERA trial.

Regarding the generalisability of the results, the company indicated the following aspects to support the applicability of the results presented to clinical practice in the UK:

- the inclusion of 13 UK study sites
- a patient population with representative baseline characteristics
- the treatment pathway reflects UK clinical practice
- the prophylactic regimens for diarrhoea in the CONTROL trial reflect UK clinical practice
- the model structure is in line with other oncology/breast cancer models
- resource use and costs were specific to the UK and validated by UK clinicians

However, a notable limitation of the current submission is the unavailability of data on overall survival.

[redacted]

ERG comment: As requested by the ERG in the clarification letter (question B2), the company provided additional details of the communication with clinical experts.[16] Table 6.7 presents an overview of how the advice received from UK clinical experts was used by the company in the development of the economic model. The company received input from clinical and health economic experts on different occasions at different stages of the development of the economic model. However, the input from the experts was not elicited through formal interview protocols and, therefore, it was not documented in a formal way.

Table 6.7: Input from UK clinical experts

Advisor - role (date)	Advice received					
	Model structure	**Identification of subsequent treatments and estimated shares in clinical practice**	**Health state resource use and costs**	**Modelling of overall survival**	**Modelling of iDFS**	**Duration of treatment effect**
Professor of Oncology at a large UK teaching hospital, principal investigator on several clinical trials (April 2017)	✓			✓	✓	
Clinical senior lecturer and honorary consultant in clinical oncology at a large UK teaching hospital, principal and chief principal investigator on many clinical trials (April 2017)	✓			✓	✓	
Consultant medical oncologist at a London hospital, chief investigator on many national and international trials (December 2018)	✓	✓	✓	✓	✓	✓

Based on response to clarification question B2[16]
iDFS = invasive disease-free survival; UK = United Kingdom

Additionally, since other important aspects of validation were not reported in the CS (e.g. quality control/verification of the calculations in the model), the ERG asked the company to provide details about what validation efforts were performed in section B.3.10 of the company submission and the results of these validation efforts (clarification question B18).[41]

The company indicated that face validity and external validity steps were described in section B.3.10 of the company submission and referred to section B.3.3.1 for the validation associated with iDFS. The company highlighted the "*importance of the iDFS extrapolation, the cross validation of alternative methods for extrapolation and the explicit use of long-term data within the extrapolation provides a key validation of the extrapolation and use of the primary endpoint from ExteNET in the model*".[16] As explained throughout section 5.2.6.1 of this report, the ERG agrees with the company in the importance of the iDFS extrapolation but considers that the company efforts on validating iDFS were insufficient.

In addition, the company mentioned that the following steps were undertaken to assess internal and cross validity. Internal validity was assessed using quality-control procedures for verification of input data. Coding was performed by staff not involved in the model development and in accordance with a pre-specified test plan. These procedures included verification of all input data used in the model with original sources and programming validation. Verification of the input data was documented in the relevant worksheets of the model. Discrepancies were discussed and the input data were updated where required. Programming validation consisted of checks of the model results, model calculations, data references, model interface and macros. The results of these internal validation efforts were not reported to the ERG. Therefore, the degree of internal validation of the model cannot be assessed. The ERG conducted additional validation efforts on the company's model but, due to the time constraints associated to this project, such efforts were limited and consisted of simple tests (e.g. whether transitions probabilities, life years, QALYs and costs are positive or not). As explained in section 7.1.2 of this report, the ERG detected negative transition probabilities. This is a very basic error and, even though it had a minor impact on the results, it was corrected by the ERG. Cross validation of the model results was not possible since there are no other economic evaluations assessing the cost effectiveness of neratinib in the extended adjuvant treatment of adult patients with early-stage HR+, HER2-overexpressed/amplified breast cancer, and who are less than one year from the completion of prior adjuvant trastuzumab-based therapy.

Finally, in clarification question B19, the ERG asked the company to provide values which can be used to validate the tails of the Markov traces obtained in the model.[16] Such values could be based on available data, literature or experts. In their response, the company referred to the HERA study as the longest (and most appropriate) available data for the UK. HERA data were used by the company in a scenario analysis but also for validating the base-case extrapolation of iDFS. Additionally, expert input from a clinical adviser confirmed that long-term survival reflective of current treatments is still unknown due to the lack of long-term data. Therefore, validating the tails of the Markov traces from the model would be speculative.

7. Evidence review group's additional analyses

7.1 Exploratory and sensitivity analyses undertaken by the ERG

7.1.1 Explanation of the company adjustments after the clarification letter

Following the clarification questions from the ERG, the company made the following four amendments to the original cost effectiveness model:

- Clarification question B22: costs of endocrine therapy were added to the model. After this change, the ICER increased by £0.35.
- Clarification question B28: the incidence of diarrhoea grade 1/2 was amended. While reviewing the model in preparation of this response, the company noticed that the change was only applied to the neratinib arm. Consequently, the company amended this in the model (see "Default Data" sheet - cell T218) to reflect a change in number of diarrhoea grade 1/2 from 6.5 to 5.2. After this change, the ICER decreased by £408.
- Clarification question C1b: correction of an error detected by the ERG. After this change, the ICER increased by £20.
- Clarification question C1c: correction of an error detected by the ERG. After this change, the ICER decreased by £2.

After all the changes made by the company, the base-case ICER decreased by £390. Therefore, the effect of these changes on the base-case ICER was minor.

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories (according to Kaltenthaler et al. 2016)[57]:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

7.1.2.1 Fixing errors

1. Error with transition probabilities in "Markov-Int" and "Markov-Comp" sheets. Depending on the parametric distribution chosen for iDFS, some cells in columns AB:AI resulted in negative transition probabilities, negative patient distribution per health states and negative life years.
2. Error with duration of adverse events. The values in the model should match those in Table 5.7 (for diarrhoea, the duration with prophylaxis should be used).

7.1.2.2 Fixing violations

3. Implementing age-adjusted utility decline from Janssen and Szende 2014.[54]

7.1.2.3 Matters of judgement

4. Treatment effectiveness:
    a. Modelling iDFS according to a stratified generalised Gamma distribution.
    b. Declining treatment effect up to month 140. This is the time point where the hazard rates of the iDFS stratified generalised Gamma distribution and the flexible Weibull (2 knots) distribution for the general population mortality. Note this is within the plausible range provided by the company (125 to 175 months), as shown in section 5.2.6.1 of this report.
5. Utilities:
    a. Trial data for iDFS health state and Lidgren et al. 2007 utilities for the other health states.[29]
6. Resource use and costs:
    a. Neratinib dose intensity equal to [redacted]%.

The main assumptions made by the company and the ERG for their preferred base-case analyses are presented in Table 7.1.

Table 7.1: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company	Justification*	ERG	Justification for change
Survival model: iDFS	ExteNET: flexible-spline Weibull with one knot General population mortality: flexible-spline Weibull two knots	Choice of extrapolation model was based on statistical goodness of fit, visual fit, clinical plausibility, and validation with external evidence.	ExteNET: stratified generalised Gamma. General population mortality: flexible-spline Weibull with two knots	Section 5.2.6.1 and section 5.2.6.3
Survival model: PDRS	Gompertz	Choice of extrapolation model was based on statistical goodness of fit and visual fit.	Gompertz	Section 5.2.6.2
Duration of treatment effect	Treatment effect was continued while patients were at increased risk of iDFS event compared with general population.	In the clinical trial, a treatment effect was maintained 4 years after treatment; extrapolations did not indicate that it would be likely for the treatment effect to disappear within the model time horizon.	Duration until hazards for general population are assumed for both treatment arms (month 140 from baseline). Treatment effect not maintained as at the end of ExteNET but tapered.	Section 5.2.6.1
Cancer-related mortality	Cancer-related mortality was only applied from distant recurrence. Mortality from all other health states was based on general population mortality.	This is in line with previous NICE appraisals, and data from ExteNET confirmed that few patients died without a distant recurrence.	Same as company.	Not changed
Proportion of local and distant recurrence between arms	Proportion of local and distant recurrence was modelled specifically per treatment arm.	Data from ExteNET showed a small difference in site of recurrence between arms.	Same as company.	Not changed

Base-case preferred assumptions	Company	Justification*	ERG	Justification for change
Time in local recurrence	Patients stayed in the local recurrence state for 12 months before being able to transition to remission.	This approach follows previous NICE assessments in which the assumption was agreed to be reasonable.	Same as company.	Not changed
HRQoL	Based on EQ-5D data collected in ExteNET and published literature. Utility values were allocated by health state and not differentiated by treatment arm.	Consistent with NICE recommendations.	ExteNET data for iDFS health state. Lidgren et al. 2007 utilities for the remaining health states.[29]	Section 5.2.8
Age adjusted utilities using Janssen and Szende 2014[54]	Not included.	Not provided and not included in the economic model	Included.	ERG critique in section 5.2.8
Dose intensity	Assumed to be [redacted]%	Based on dose holds and dose reductions in the ExteNET label population	Base-case: [redacted]% Scenario: [redacted]%	ERG critique section 5.2.9.1
Treatment duration	Assumed to be [redacted] months (rather than the prescribed 12 months)	Based on treatment discontinuations in the ExteNET label population	Base-case: [redacted] months Scenario: 12 months	ERG critique section 5.2.9.1
Costs of endocrine therapy	Not included		Included	Endocrine therapy should be costed as 98% of patients are receiving it

* Based on Table 54 of the CS[1]

CS = company submission; EQ-5D = European Quality of Life-5 dimensions; ERG = Evidence Review Group; HRQoL = health-related quality of life; iDFS = invasive disease-free survival; NICE = National Institute for Health and Care Excellence; PDRS = post-distant recurrence survival

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted several additional scenario analyses in which the main sources of uncertainty identified by the ERG were explored. These were the uncertainties associated with modelling iDFS (parametric curve selection and treatment effect), the source of input data for utilities and the duration and dose of treatment with neratinib. Other sources of uncertainty were deemed less important (see e.g. Table 6.6) and were not explored in this section. A list of the scenario analyses conducted by the ERG is provided below.

7.1.3.1 Scenario set 1: changing iDFS parametric distributions

As explained in section 5.2.6.1 of this report, the ERG identified three main sources of uncertainty associated to modelling iDFS:

1. The selection of the parametric curves to extrapolate iDFS beyond the trial follow-up.
2. The type of treatment effect: maintained after trial follow-up or tapered.
3. The duration of the treatment effect.

The company presented only one an alternative scenario where the parametric curve for iDFS was changed (Gompertz) compared to the base-case (flexible Weibull [one knot]). As explained in section 5.2.6.1 of this report, the ERG considered that the company should have considered other parametric distributions. In particular, the ERG explored four additional scenarios assuming a stratified flexible Weibull (one knot), a flexible Weibull (one knot), a flexible Weibull (two knots) and a generalised Gamma distribution for modelling iDFS.

Furthermore, the ERG considered a tapering of the treatment effect more plausible than a treatment effect that is maintained after the trial follow-up period (the latter was assumed by the company). The ERG assumed the (maximum) taper period corresponds to the time point when the placebo hazard rate equals the general population mortality hazard rate. This point depends on the curve chosen for iDFS. Therefore, for each distribution the taper period is different. Thus, in each of these scenarios, besides selecting a different iDFS curve in the model, a different length of the tapering period has to be inputted too.

7.1.3.2 Scenario set 2: changing the duration of the treatment effect

For all these scenarios the iDFS distribution is not changed. The distribution chosen is the same as in the ERG base-case: the stratified generalised Gamma. As explained in section 5.2.6.1 of this report, the maximum taper period for this distribution was 140 months. This was calculated following the ERG assumption that the maximum taper period corresponds to the point when the placebo hazard rate equals the general population mortality hazard rate. The ERG conducted a series of "what if" scenarios where the taper period was assumed to be shorter than 140 months. An additional scenario assuming a continued treatment effect after trial follow-up was also conducted.

7.1.3.3 Scenario set 3: utilities

In this set of scenarios, the ERG explored the impact of using different sources for the utility estimates on the model results. The ERG also studies the effect of not considering an age-related utility decrement in the economic analyses.

7.1.3.4 Scenario set 4: neratinib treatment duration and dose intensity

In the company base-case, the assumed treatment duration for neratinib was [redacted] months at [redacted]% dose intensity. Dose intensity and treatment duration were based on data from ExteNET, in which a

relatively larger proportion of patients withdrew from or withheld treatment due to adverse events, most notably diarrhoea, than would be expected with the use of prophylaxis for diarrhoea (i.e. as in CONTROL). Therefore, the ERG assessed the impact on the cost effectiveness results of assuming different dose intensities and treatment durations.

7.1.3.5 Scenario set 5: transition probability from remission to distant recurrence

In the company base-case, the probability of transition from the remission health state to the distant recurrence health state was fixed and equal to 0.757% as in TA569.[25] Since no other sources of evidence to inform this parameter were available, the ERG simply assumed half and double this value and assessed the impact of changing this probability on the model results.

7.1.3.6 Scenario set 6: proportions of patients with local recurrence

In the company base-case, the proportions of patients with local recurrence are based on data from ExteNET (18% for neratinib, and 31% for placebo). In this series of scenarios, the ERG assessed the impact of different assumptions regarding the proportions of patients with local recurrence. In particular, a difference in + and – 5% for each arm was assumed.

7.1.3.7 Scenario set 7: cost of distant recurrence

In the company base-case, the cost of distant recurrence was assumed to be £175,390. This value was taken from the TA569 appraisal.[25] The subsequent treatments which patients would be expected to receive and the relative treatment shares of treatments identified were also explored by the company in the expert elicitation process. Treatments and treatment shares identified through expert elicitation differed somewhat from those obtained from TA569.[25] In the clarification stage the ERG requested that the values from expert elicitation be incorporated into an alternative scenario in the model. The company declined and therefore alternative values have been explored in this scenario analysis.

7.1.3.8 Scenario set 8: post distant recurrence survival

In the base-case, a Gompertz distribution was assumed to model PDRS. As explained in section 5.2.6.2 of this report, the fit seems poor in general and based on the AIC and BIC values, the ERG explored three additional scenarios assuming an exponential, a Gamma and a Weibull distribution for modelling PDRS.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

7.2.1 Results of the ERG preferred base-case scenario

The results of the ERG preferred base-case analysis (as outlined in section 7.1.2 of this report) are displayed in Table 7.2. The implementation of the ERG preferred assumptions resulted in an ICER of £46,298, which is nearly double the company's original base-case ICER of £24,585.

Table 7.2: ERG preferred deterministic base-case results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Neratinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Placebo	[redacted]	[redacted]	[redacted]				

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALY = quality-adjusted life year

A PSA was also conducted using the ERG preferred base-case assumptions. The results of the ERG PSA are shown in Table 7.3. The probabilistic ICER was £49,134, which is slightly higher than, but still in line with, the deterministic ICER.

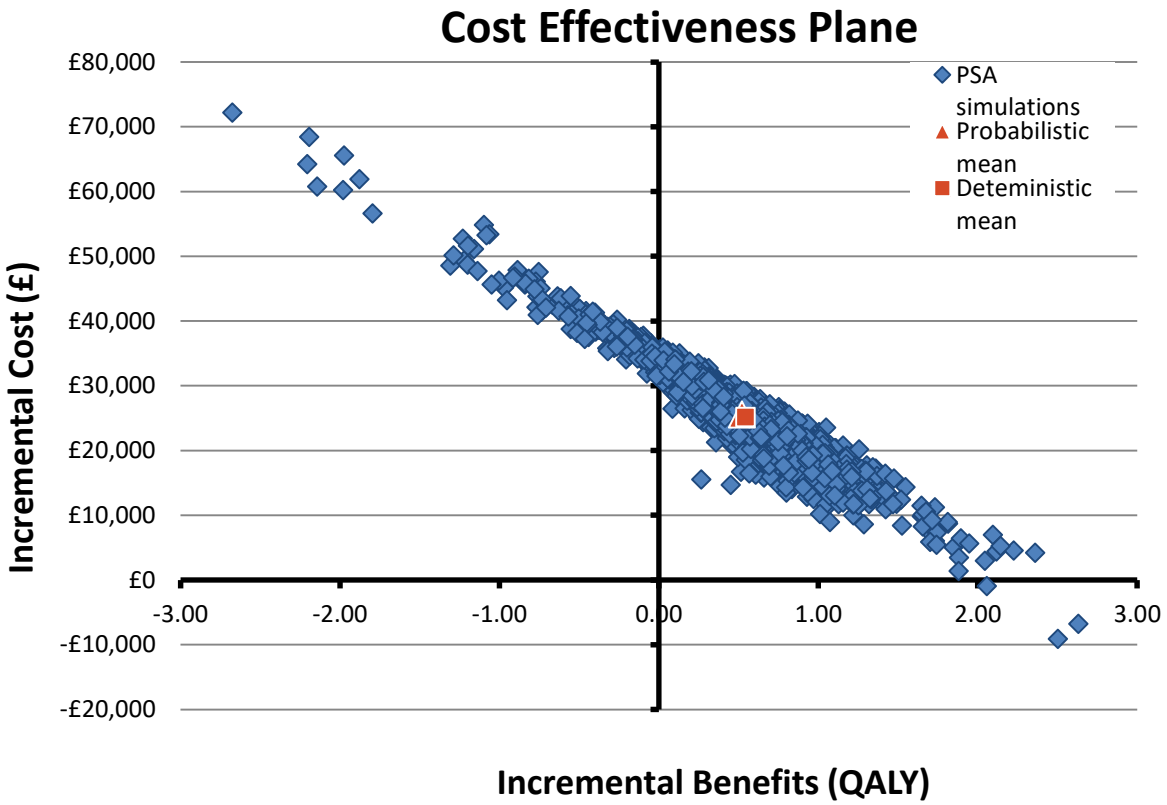
Table 7.3: ERG base-case probabilistic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Placebo	[redacted]	[redacted]			
Neratinib	[redacted]	[redacted]	[redacted]	[redacted]	£49,134

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year

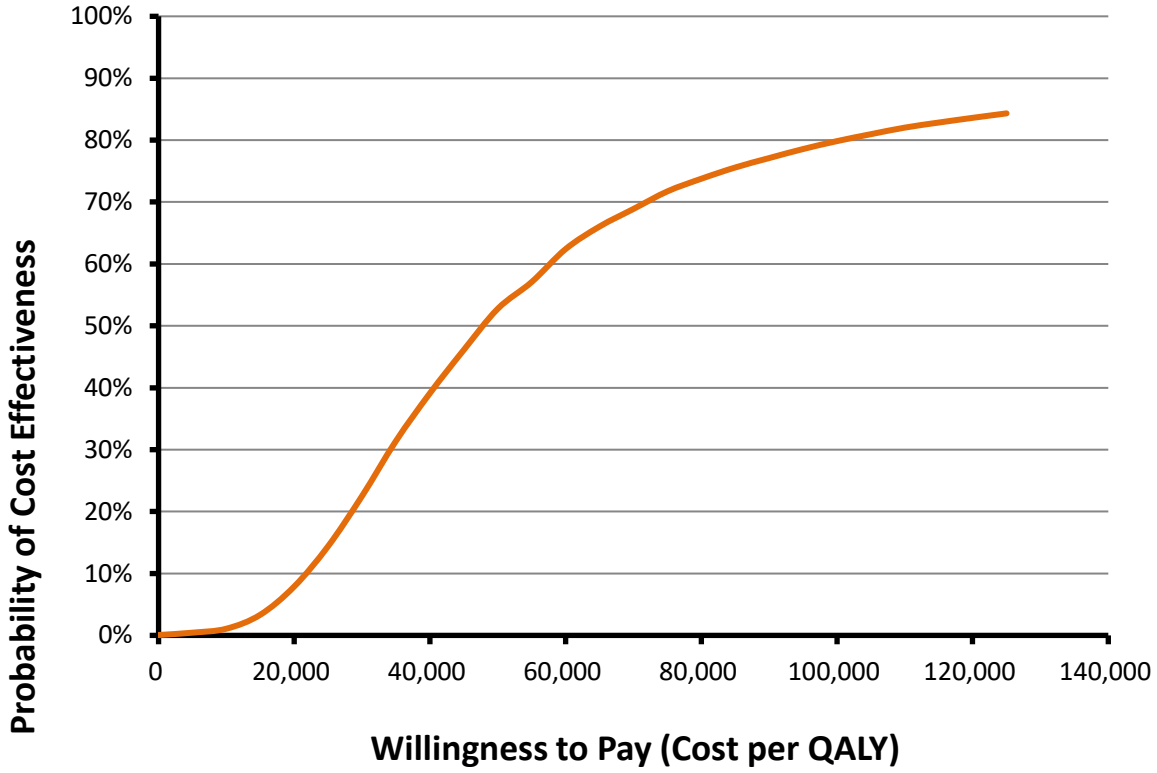
The incremental costs and incremental QALYs obtained from the ERG PSA were plotted in the CE-plane and a cost effectiveness acceptability curve (CEAC) was calculated. These are shown in Figures 7.1 and 7.2, respectively. Most of the simulations ([redacted]%) fell in the north-east quadrant of the CE-plane, where neratinib provides additional QALYs to placebo, but at additional costs. Placebo dominated neratinib in the north-west quadrant of the CE-plane in [redacted]% of simulations. Neratinib dominated placebo in [redacted]% of simulations in the south-east quadrant of the CE-plane. The CEAC indicated that at WTP thresholds of £20,000 and £30,000, the probability that neratinib is cost effective is 7.9% and 22.5%, respectively.

Figure 7.1: ERG preferred cost effectiveness plane



Based on electronic model
ERG = Evidence Review Group; QALY = quality-adjusted life year

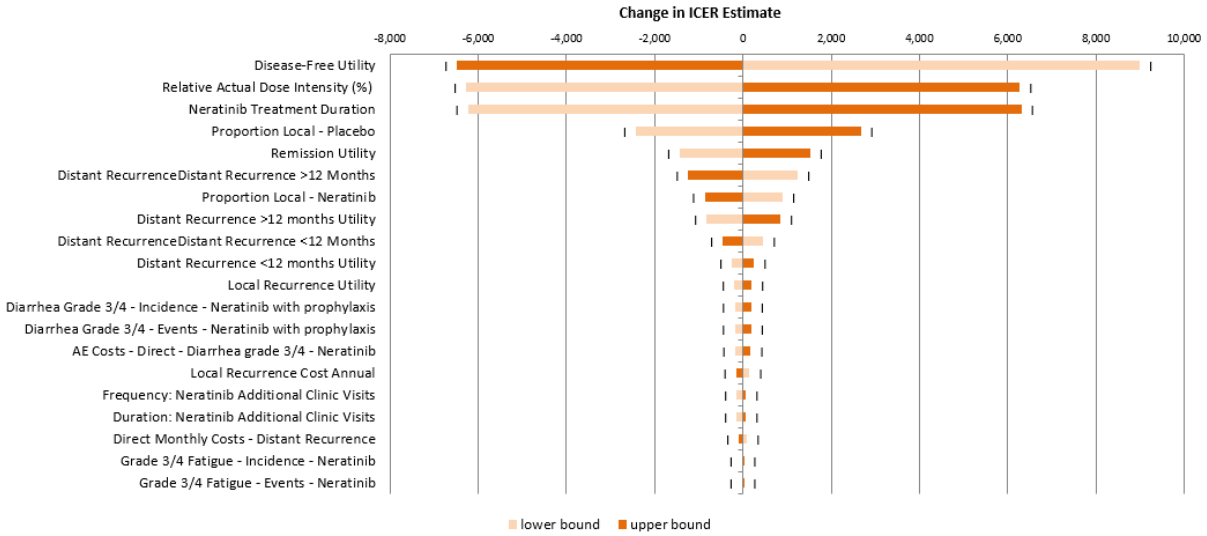
Figure 7.2: ERG preferred cost effectiveness acceptability curve



Based on electronic model
ERG = Evidence Review Group; QALY = quality-adjusted life year

The ERG also conducted an OWSA based on their preferred base-case assumptions. As can be seen from the tornado diagram in Figure 7.3, assumptions surrounding the disease-free health state utility value, relative actual dose intensity of neratinib and neratinib treatment duration still have the largest impact on the ICER. However, following changes to the company base-case assumptions, the uncertainty surrounding the disease-free utility value has increased in importance to overtake the uncertainty surrounding dose intensity and treatment duration.

Figure 7.3: Tornado diagram – ERG's preferred assumptions



Based on electronic model

AE = adverse event; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio

7.2.2 Results of the ERG additional exploratory scenario analyses

7.2.2.1 Additional scenario 1: changing iDFS parametric distributions

In this series of scenarios, the ERG assessed the impact of using different parametric survival curves for extrapolating of iDFS beyond the duration of the ExteNET trial. In Table 7.4, the results are displayed indicating the corresponding taper period for each distribution. Note the total duration of the treatment effect is calculated as the total follow-up time in ExteNET (62.98 months) plus the taper period (e.g. in the ERG base-case this was 77.02 months, so the total duration of the treatment effect was 140 months). The difference between the highest and the lowest ICER was £43,690. However, the scenario with the largest ICER (£80,818) was obtained assuming a generalised Gamma distribution, which was criticised by the company as mentioned in section 5.2.6.1. For the remaining three scenarios the ICERs are approximately £38,000 with plausible taper periods.

Table 7.4: ERG iDFS scenario analyses

Distribution [taper period in months]	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Stratified generalised gamma [77.02]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Stratified flexible Weibull (1 knot) [234.02]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,128
Flexible Weibull (1 knot) [113.02]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,178
Flexible Weibull (2 knots) [111.02]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,448
Generalised Gamma [76.02]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£80,818

Based on electronic model
*ERG preferred base-case
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year

7.2.2.2 Additional scenario 2: changing the duration of the treatment effect

In all these scenarios the iDFS distribution was the stratified generalised Gamma as in the ERG base-case. The maximum taper period for this distribution was 140 months. In this series of scenarios, the ERG assessed the impact of assuming different (shorter) taper periods. In Table 7.5, the results are shown taper periods of 0 (i.e. no continuation of treatment effect), 12, 24, and 60 months after the end of ExteNET follow-up. Additionally, a scenario assuming a continued treatment effect after trial follow-up was also conducted. As expected, the ICER decreased when the assumed duration for the taper period (treatment effect) increased. Thus, assuming no treatment effect after the trial period resulted in an ICER of £56,871 and when a continued treatment effect was assumed (i.e. no tapering but constant treatment effect) the ICER was £42,392.

Table 7.5: ERG duration of the treatment effect scenario analyses

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Taper period of 0 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,871
Taper period of 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,175
Taper period of 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,150
Taper period of 60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,785
Taper period of 77.02 months*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Continued treatment effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,392

Based on electronic model
* ERG preferred base-case
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year

7.2.2.3 Additional scenario 3: utilities

In this series of scenarios, the ERG assessed the impact of using different assumptions and values for utilities. In the first scenario explored by the ERG, the effect of not considering an age-related utility decrement in the economic analyses was studied. In the other two scenarios, the age-related utility decrement was assumed but the set of utility values were changed. First the set of utilities used in the company base-case was chosen and then the utilities from Lidgren et al. 2007 were selected.[29] Results are presented in Table 7.6. The scenario with the ERG preferred utilities but no age-related decrements resulted in the lowest ICER (£42,050), while the scenario where the utilities from Lidgren et al. 2007 were used resulted in the highest ICER (£50,912).[29]

Table 7.6: ERG utility scenario analyses

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
No age-related utility decrement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,050
Utility set as in company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,848
Utility set from Lidgren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,912

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
et al. 2007[29]							
Based on electronic model ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year							

7.2.2.4 Additional scenario 4: neratinib treatment duration and dose intensity

In this series of scenarios, the ERG assessed the impact of assuming different treatment durations and dose intensities for neratinib on the cost effectiveness results. In Table 7.7, the results are shown for the scenarios assuming a dose intensity of [redacted]%, a dose intensity as in the company base case ([redacted]%), a treatment duration of 12 months, a treatment duration of 10.05 months (halfway between [redacted] and 12 months), and the combination of a dose intensity of [redacted]% with a treatment duration of 12 months (as 'prescribed per protocol'). As expected, the ICER increased with increased dose intensity and treatment duration. Thus, assuming the dose intensity and treatment duration observed in ExteNET, as in the company base-case, resulted in the lowest ICER (£42,168). When the neratinib dose intensity and duration were considered as prescribed, the ICER was £81,962. The difference between the highest and the lowest ICER was then £39,794, which indicates a considerable level of uncertainty associated with the model results.

Table 7.7: ERG treatment duration and dose intensity scenario analyses

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Dose intensity [redacted]%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,422
Dose intensity as in company base case ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,168
Treatment duration of 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£75,896
Treatment duration of 10.05 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£61,265
Dose intensity [redacted]% + treatment duration of 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,962
Based on electronic model ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year							

7.2.2.5 Additional scenario 5: transition probability from remission to distant recurrence

In the company base-case, the probability of transition from the remission health state to the distant recurrence health state was fixed and equal to 0.757%. The results of the scenarios assuming half (0.3785%) and double (1.514%), these values are shown in Table 7.8. Halving the transition probability resulted in an ICER increased by £7,727. When the transition probability was doubled the ICER was decreased by £5,585.

Table 7.8: ERG scenario cost effectiveness results using different transition probabilities for the transition from remission to distant recurrence

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
TP = 0.3785%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,025
TP = 1.514%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,713

Based on electronic model
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year, TP = transition probability.

7.2.2.6 Additional scenario 6: proportions of patients with local recurrence

In this series of scenarios, the ERG assessed the impact of different assumptions regarding the proportions of patients with local recurrence. In the base case analysis, these are based on data from ExteNET (18% for neratinib, and 31% for placebo). In Table 7.9 the results are shown for assuming + and – 5% for each. The fluctuation between 13% and 23% in the neratinib group had a £4,836 impact on the ICER while the 10% fluctuation in the placebo group had a £8,369 impact on the ICER.

Table 7.9: ERG scenario cost effectiveness results using different proportions of patients with local recurrence

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Neratinib: 13% local	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,002
Neratinib: 23% local	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,166
Placebo: 26% local	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,632
Placebo: 36% local	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,001

Based on electronic model
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year

7.2.2.7 Additional scenario 7: cost of distant recurrence

In this series of scenarios, the ERG explored the impact of assuming different costs associated to distant recurrence. In the company base-case, the cost of a distant recurrence was assumed to be £175,390. In these two scenarios, explored the impact of increasing and decreasing this value by (approximately) £25,000. Results are shown in Table 7.10. When the cost of distant recurrence was increased to £200,000, the ICER was reduced by £2,376 to £43,922. When the cost of distant recurrence was decreased to £150,000, the ICER was increased by £2,452 to £48,750.

Table 7.10: ERG cost of distant recurrence scenario analyses

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Cost of distant recurrence £200,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,922
Cost of distant recurrence £150,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,750

Based on electronic model
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year

7.2.2.8 Additional scenario 8: post distant recurrence survival

In these scenarios, the ERG explored the impact of assuming an exponential, a Gamma and a Weibull distribution for modelling PDRS. The results shown in Table 7.11 suggested that the choice of the parametric distribution for PDRS has a minor impact on the ICER, which at most increased by £2,117 compared to the ERG base-case.

Table 7.11: ERG PDRS scenario analyses

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Gompertz*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,415
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,331
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,738

Based on electronic model
* ERG preferred base-case
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year

7.3 ERG's preferred assumptions

The ERG preferred changes to the updated company base-case were described in section 7.1.2 of this report. The cost effectiveness results of the ERG preferred base-case are presented in Table 7.12 in eight steps, where, in each step, the cumulative impact on the model results is shown. The assumption

with the largest impact on the ICER was the choice of the stratified generalised Gamma function to model iDFS. This results in an ICER increased by £9,660. All the other changes made by the ERG also resulted in increasing the ICER but in all cases the increase was less than £5,000. The base-case ICER in the company submission was £24,585. The ICER based on the ERG preferred assumptions was £46,298.

Table 7.12: ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Neratinib		Placebo		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,585
Company updated base-case (after clarification)	7.1.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,194
ERG change 1 – Correcting negative transition probabilities	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,283
ERG change 3 – Correcting duration of adverse events	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,269
ERG change 4 – Implementing age-adjusted utility decline from Janssen and Szende 2014.[54]	5.2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,784
ERG change 5 – Modelling iDFS according to a stratified generalised Gamma distribution	5.2.6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,444
ERG change 6 – Declining treatment effect up to month 140	5.2.6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,936
ERG change 7 – ExteNET utilities for iDFS (and remission) health state and Lidgren utilities for the remaining health states	5.2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,168
ERG change 8 – Neratinib dose intensity equal to [redacted]%.	5.2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,298

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

7.4 Conclusions of the cost effectiveness section

The company developed a *de novo* Markov model to evaluate the cost effectiveness of neratinib compared to standard treatment with no further HER2-directed therapy. Patients start the simulation in the iDFS health state where they receive neratinib or standard treatment. From the iDFS health state, patients can transition to local recurrence, distant recurrence or dead. Local recurrence is a tunnel health state in which patients receive adjuvant therapy until they transition to remission or dead. Patients who transition to remission can stay in that health state, or move to distant recurrence or dead. From all health states, patients can transition to dead. From iDFS, local recurrence and remission, patients die according to general population mortality risks. Mortality from the distant recurrence health state was modelled assuming the post distant recurrence mortality risk (based on blinded survival data) obtained from both arms of the ExteNET trial. Costs and utilities allocated to the health states of the model (except dead) are used to calculate expected total costs and total QALYs per model cycle.

The company used data from the ExteNET label population to inform iDFS parameters in the model. Mortality from distant recurrence was modelled using the blinded PDRS data (ITT population) from both arms of the ExteNET trial. Patients experiencing a local recurrence were assumed to stay in the local recurrence health state for one year, in which they receive additional adjuvant therapy. After that, they either transition to the remission health state or die (due to all-cause mortality). In the remission health state, patients can either die from all-cause mortality or experience another recurrence. A constant monthly transition probability from remission to distant recurrence was assumed. Death due to breast cancer is only possible from the distant recurrence health state. For all the other health states, mortality risk was modelled according to age-adjusted survival probabilities for the female general population.

Incidence and mean number of AEs were taken from the label population of the ExteNET trial, with the exception of diarrhoea (with prophylaxis), which were taken from the CONTROL trial safety population (who were mandated loperamide alongside neratinib). Utility decrements and costs associated with AEs were then estimated per AE episode and applied once at the beginning of the simulation based on the proportion of patients in each treatment arm experiencing AEs.

The company used a generalised linear mixed model (fitted with data from the label population in ExteNET) to derive utility values for the iDFS health state. The utility value for the remission health state was assumed to be equal to iDFS. The utility values for local and distant recurrence were taken from previous NICE submissions in similar indications. Utility decrements associated with adverse events were also sourced from the literature (including prior NICE appraisals).

The model included treatment costs for neratinib and standard treatment (placebo). Neratinib intervention costs included drug acquisition, including prophylaxis for diarrhoea with loperamide, and additional monitoring (liver function tests and GP visits). Intervention costs in the placebo arm consisted of endocrine therapy (also given as concomitant therapy in neratinib patients) with unit costs obtained from eMIT. Resource use associated with breast cancer consisted of GP, oncologist social worker and clinical nurse specialist visits, district nurse home visits, mammograms and ECHO, MUGA and CT scans. The company reviewed existing NICE appraisals in similar populations and sought expert opinion to estimate expected resource use specific to each health state in the model. Unit costs for the resources identified were obtained from NHS Improvement,[33] NICE clinical guidelines for familial breast cancer [34] and Curtis and Burns 2018.[32] Adverse event costs were obtained from NHS Improvement [33] and inflated according to Curtis and Burns 2018.[32] Assumptions regarding subsequent treatments following recurrence were taken from the NICE appraisal of

pertuzumab (TA569) for adjuvant treatment of early HER2+ breast cancer.[25] Treatments were divided into those relevant for non-metastatic (local) recurrence, first-line early metastatic (distant) recurrence and second-line early metastatic (distant) recurrence. Costs of the drugs identified were taken from the eMIT and BNF databases.[55, 56] Drug doses were estimated according to the mean body surface area (1.80 m^2) and weight (72.64 kg) of patients from the ExteNET label population. Administration costs for identified subsequent treatments were taken from the NHS Reference Costs.[33]

The discounted base-case results indicated that, compared with placebo, neratinib generated [redacted] incremental QALYs, and [redacted] incremental LYGs, with (higher) incremental costs of [redacted]. Thus, the ICER was £24,585 per QALY gained. The company also conducted a probabilistic and a one-way sensitivity analysis, and a number of additional scenario analyses. The probabilistic ICER was £24,413 per QALY gained. The majority of the 5,000 iterations provided results in the north-east quadrant of the CE plane. The CEAC showed that neratinib has a 36% probability of being cost effective at a threshold of £20,000 per QALY and a 60% probability of being cost effective at a threshold of £30,000 per QALY. The results of the one-way deterministic sensitivity analysis indicated that the relative prescribed dose intensity of neratinib, the neratinib treatment duration and the assumed utility of the disease free (and remission) health state have the largest impact on the ICER. The results of the scenario analyses suggested that that the model is robust to most of the assumptions tested by the company. The scenario with the largest impact on the ICER was obtained by replacing the assumption of no treatment effect waning at the end of the trial (except for earlier crossover to general population mortality for neratinib arm) with the assumption that the treatment effect waned to no treatment effect 13.9 years post-randomisation. This caused the ICER to increase to £31,677.

The structure of the conceptual model for this submission was similar to that taken in the NICE appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer.[25] The main differences and similarities between the economic model used for the current submission and the model used for the pertuzumab appraisal (TA569) were summarised in section 5.2.2 of this report. Concerns about the absence of OS data (per treatment arm) and the narrower definition used for iDFS, as discussed in the clinical effectiveness sections, also apply to the cost effectiveness model.

In the absence of treatment-specific OS data, the company assumed the same mortality rate as the general population for the health states of iDFS, local recurrence and remission. Only for the health state of distant recurrence is the mortality rate higher. It is very likely that the mortality rate has, therefore, been underestimated for those three states and, given that the difference between neratinib and standard care is in iDFS, this is likely to overestimate the life expectancy gain to neratinib, although, given the lack of OS data, the size of this bias is impossible to estimate.

The ERG considers that there is uncertainty regarding the assumption of proportional hazards for iDFS and, therefore, other options should have been considered in the economic analyses as well. The selection of parametric models should have been broader and should have included both proportional and non-proportional hazards models. Regarding the treatment effect, the company assumed for the base-case analysis that the treatment effect observed at the end of the five-year follow-up was maintained until the patients had equal risk of an iDFS event as the general population. This implicitly means that there is a waning of the treatment effect starting at month 130 with a taper of effect over the next 3.83 years (month 176) at which point no further treatment effect is included in the model. The ERG does not agree with this choice and considers that a more rapid waning in the treatment effect is more plausible.

Based on the PDRS information presented by the company (visual assessment of the KM and survival parametric curves, AIC and BIC goodness-of-fit statistics), the ERG agrees with the choices made by the company for the base-case. However, the visual fit looks poor in general and it is difficult to decide what distribution provides a better fit.

The incidence and mean number of events of diarrhoea with prophylaxis using loperamide was obtained from the safety population of the CONTROL trial. This population does not match the ExteNET label population in terms of length of time from trastuzumab or HR status. The company indicated that 73% of the CONTROL loperamide group matched the criteria for the label population and that they were not aware of any clinical reason why the effect of diarrhoea prophylaxis would differ between the safety and label population.

The ERG has concerns regarding the utility value obtained for the iDFS health state. While the initial objective of the company was to obtain utility estimates for all health states in the model, only data from patients in the iDFS health state were considered for that analysis. This might be related to a protocol amendment that removed the requirement to collect HRQoL data. The result was a dataset that is incomplete and not fit for the purpose of the analysis (i.e. to obtain utility values for each health state in the model). The company indicated that any estimates derived from this analysis should be interpreted with caution due to the presence of cases with missing values. Although the issue with missing values was mentioned in relation to unexpected and counterintuitive results on the impact of different grades of diarrhoea on HRQoL, the same model was used to estimate the utility value for iDFS. The mixed models used by the company can accommodate missing values but only under the assumption that data is missing at random can the results be considered unbiased. That assumption might be questionable here (e.g. patients who are worst off are the first to stop filling in the EQ-5D). Therefore, similar concerns to those raised by the results for diarrhoea may also apply to the iDFS utility. For these reasons, the ERG has limited confidence in relying on the use of this utility value for iDFS to assess the cost effectiveness of neratinib. The second concern regarding utilities is the possible impact of mixing data sources to estimate utility values for the other health states in the model since these are not based on empirical data from the same study. Finally, the company did not include age-related utility decrements in the model, despite reporting an indication of changes in utility over time. This decision was based on analysis results being non-significant and following an unclear pattern. However, since the overall utility of the general population is expected to decrease in time, the ERG considers it plausible to incorporate in the economic analysis an age-based decline in utilities.

The ERG has also concerns surrounding the calculation of treatment duration and relative actual dose intensity used in the model. In the company submission, it is stated that in the CONTROL trial, where prophylaxis was mandated alongside neratinib, diarrhoea related dose holds and dose reductions were lower than in the ExteNET trial, where prophylaxis was not mandated. Therefore, the ERG considers that the value for relative actual dose intensity ([redacted]%) and resulting treatment cost incorporated into the company base-case are likely to be lower than would be observed in clinical practice, if prophylaxis with loperamide is expected. The introduction of prophylaxis for diarrhoea may also be expected to reduce AE related discontinuations. However, this was not observed in the comparison between the ExteNET and CONTROL discontinuation rates provided by the company, where the AE related withdrawals in CONTROL were higher (which seems to contradict the results regarding AE related dose reductions and holds).

Following the clarification questions from the ERG, the company made four amendments to the original model. The list of amendments is provided in section 7.1.1 but the effect of these changes on

the base-case ICER was minor. Additionally, the ERG corrected two errors found in the model (with a minimal impact on the results) and made the following changes to the model received with the response to the clarification letter: 1) implementing age-adjusted utility decline from Janssen and Szende 2014,[54] 2) modelling iDFS according to a stratified generalised Gamma distribution, 3) declining the neratinib treatment effect from month 63 (end of ExteNET trial follow-up) to month 140 (instead of considering it maintained), 4) using utility data for the iDFS health state from the ExteNET trial and from Lidgren et al. 2007 for the other health states and 5) assuming a neratinib dose intensity equal to [redacted]%.[29] The ERG preferred base-case analysis resulted in an ICER of £46,298, which was nearly double the company's original base-case ICER of £24,585.

A PSA and an OWSA were also conducted using the ERG preferred base-case assumptions. The probabilistic ICER was £49,134, which was slightly higher, but still in line with, the deterministic ICER. Most of the simulations ([redacted]%) fell in the north-east quadrant of the CE-plane. Placebo dominated neratinib in the north-west quadrant of the CE-plane in [redacted]% of simulations. Neratinib dominated placebo in [redacted]% of simulations in the south-east quadrant of the CE-plane. The CEAC indicated that at WTP thresholds of £20,000 and £30,000, the probability that neratinib is cost effective is 7.9% and 22.5%, respectively. The results of the OWSA indicated that the disease-free health state utility value, relative actual dose intensity of neratinib and neratinib treatment duration still have the largest impact on the ICER. However, the way the OWSA was conducted, allowing 10% variation from mean value for all parameters, seems arbitrary and may not represent an equally plausible range of variation for all input parameters. Whenever possible, the limits of (95%) confidence intervals should be used for each parameter to calculate the upper and lower bounds of the bars in the tornado diagram. Given the time constraints associated with this project, the ERG was not able correct this in the model. Therefore, the ERG considers that the tornado diagram (Figure 7.3) should be interpreted with caution.

The ERG considered that the scenario analyses conducted by the company were insufficient to draw overall conclusions on the robustness of the model results. For example, the company should have considered a wider range of distributions to model iDFS. Assumptions regarding the type and duration of the neratinib treatment effect, the source of utility data, the duration of neratinib treatment or the neratinib dose intensity should have been extensively explored, since these are expected to influence the model results. Therefore, the ERG conducted several additional scenario analyses to explore several sources of uncertainty that seem to be relevant for the model results identified by the ERG. From the results of these analyses it could be concluded that the ICER was most sensitive to changes in the selection of parametric survival curves for extrapolating of iDFS beyond the duration of the ExteNET trial (including the duration and type of treatment effect) and the assumptions about treatment durations and dose intensities for neratinib. When assessing the impact of using different parametric survival curves for extrapolating of iDFS, it was observed that the difference between the highest and the lowest ICER was £43,690. However, the scenario with the largest ICER (£80,818) was obtained assuming a generalised Gamma distribution, which was criticised by the company as mentioned in section 5.2.6.1. For the three remaining scenarios, the ICERs are approximately £38,000 with plausible taper periods. In a different set of scenarios, the iDFS distribution was fixed as in the ERG base-case (stratified generalised Gamma). The maximum taper period for this distribution was 140 months. Different (shorter) taper periods of 0 (i.e. no continuation of treatment effect), 12, 24, and 60 months after the end of ExteNET follow-up were assumed. Additionally, a scenario assuming a continued treatment effect after trial follow-up was also conducted. The ICER decreased when the assumed duration for the taper period (treatment effect) increased. Thus, assuming no treatment effect after the trial period resulted in an ICER of £56,871 and when a continued treatment effect was

assumed (i.e. no tapering but constant treatment effect) the ICER was £42,392. The impact of assuming different treatment durations and dose intensities for neratinib on the cost effectiveness results was also assessed by the ERG. In particular, scenarios assuming a dose intensity of [redacted]%, a dose intensity as in the company base case ([redacted]%), a treatment duration of 12 months, a treatment duration of 10.05 months (halfway between [redacted] and 12 months), and the combination of a dose intensity of [redacted]% with a treatment duration of 12 months (as 'prescribed per protocol') were conducted. The ICER increased with increased dose intensity and treatment duration. Thus, assuming the dose intensity and treatment duration observed in ExteNET, as in the company base-case, resulted in the lowest ICER (£42,168). When the neratinib dose intensity and duration were considered as prescribed, the ICER was £81,962. The difference between the highest and the lowest ICER was then £39,794, which indicates a considerable level of uncertainty associated with the model results. Despite the ERG concerns regarding the utilities described in section 5.2.8, the impact of using different assumptions and values for utilities was not large. The scenario with the ERG preferred utilities but no age-related decrements resulted in the lowest ICER (£42,050), while the scenario where the utilities from Lidgren et al. 2007 were used resulted in the highest ICER (£50,912).[29] Therefore, it is possible that the uncertainties associated with the utilities (structural and input data uncertainty associated with the estimation of a generalised linear mixed model based on an incomplete dataset) are not captured in the current economic analyses. Finally, other scenarios explored by the ERG considered alternative assumptions on the probability of transition from the remission health state to the distant recurrence health state, the proportions of patients with local recurrence, the costs associated to distant recurrence and the choice of different distributions for the extrapolation of PDRS. However, the impact on the results was minor compared to the previously described uncertainties.

8. End of life

According to Table 1 of the CS, *"Neratinib is not considered by the company to meet NICE End of Life criteria"*.[1]

9. References

[1] Puma Biotechnology. *Neratinib (NERLYNX®) for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab [ID981]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission*: Puma Biotechnology, 2019. 147p.

[2] National Institute for Health and Clinical Excellence. *Neratinib for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab [ID981]. Final scope [Internet]*. London: National Institute for Health and Clinical Excellence, 2019 [accessed 6.2.19] Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10107/documents

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Appendix 1: ERG search strategies

Additional limitations of the CS searches not covered in the main body of the report:

Clinical effectiveness

- There is a typographical error in line #8 of all Medline/Medline In Process searches: '[Tet Word]' should read '[Text Word]'.
- It is incorrect to state that updates of DARE were conducted in November 2018 on the Cochrane Library interface, as it was removed from the Cochrane Library in August 2018. However, no new records were added to DARE from March 2015, so this will not have affected the overall results.
- It is not clear in the Cochrane Library searches undertaken in November 2016 and February 2018 what results were found on which of the included databases (CDSR/CENTRAL/DARE).

Cost effectiveness

- The Cochrane Library searches have been presented in a non-standard manner. The final line of the search combines sections 1, 2, 3 and 4 of the strategy, however if the search string used was entered as displayed into the Cochrane Library it would translate incorrectly as a line combination. Although the results appear to be correct, it is not good practice to report search strategies in this way, and does not make the strategy easily reproducible. As recommended in the Cochrane Handbook[23] 'search strategies should be copied and pasted exactly as run and included in full together with the line numbers for each search set. They should not be re-typed as this can introduce errors.
- It is incorrect to state that updates of DARE, NHS EED and the HTA database were conducted in November 2018 on the Cochrane Library interface, as all three databases were removed from the Cochrane Library in August 2018. However, no new records were added to DARE or NHS EED from March 2015 or to the HTA database from March 2018, so this will not have affected the overall results.

Appendix 2: Standard parametric models fitted to the ExteNET trial data: disease-free survival: trastuzumab therapy completed within the past 12 months: HR+

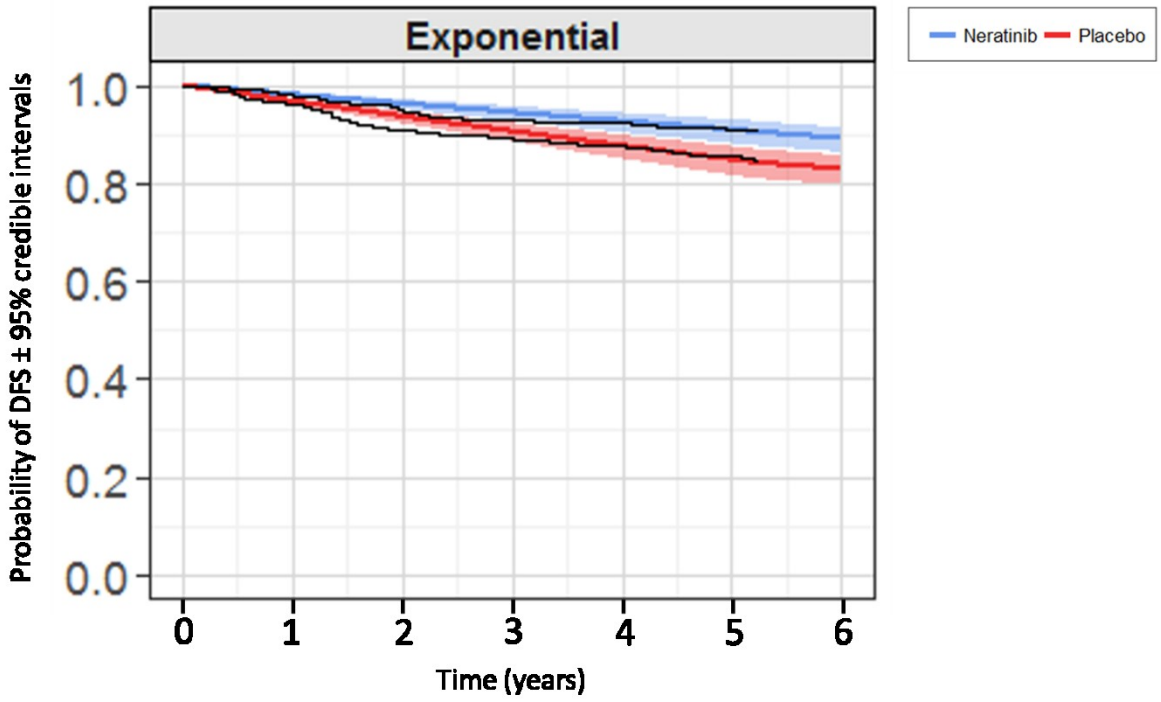
In response to the clarification question B11, the company provided the different parametric models fitted to the ExteNET trial data in Figures 5.8 and 5.9 of this report, separately. These are shown below as presented in response to the clarification letter.[16]

Based on Figure A3.10, the company concluded that at the end of the trial follow-up for EXTENET the generalised gamma distribution underestimated the KM curve for the neratinib arm and overestimated the placebo arm. The good fit based in AIC or BIC is, according to the company, likely to result from a good fit to the early part of the trial data.

Therefore, the company considered that extrapolations based on the generalised gamma are likely to result in over predictions of placebo and under prediction of neratinib long-term survival. From examining all distributions, the generalised gamma is, according to the company, a clear outlier towards the end of the trial follow-up with the poorest visual fit to the later part of the KM data for both arms.

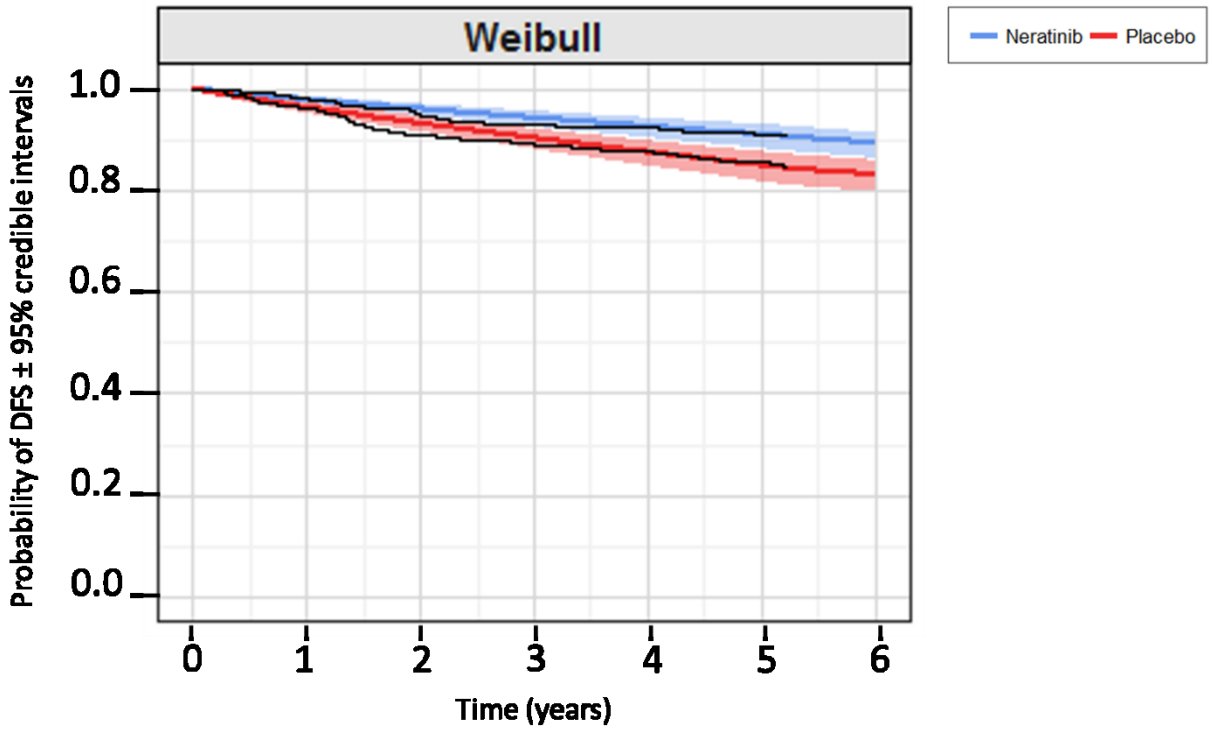
As mentioned in the section 5.2.6.1, the ERG is more neutral regarding the assessment of visual fit with KM curves, even using these enlarged plots.

Figure A2.1: Exponential



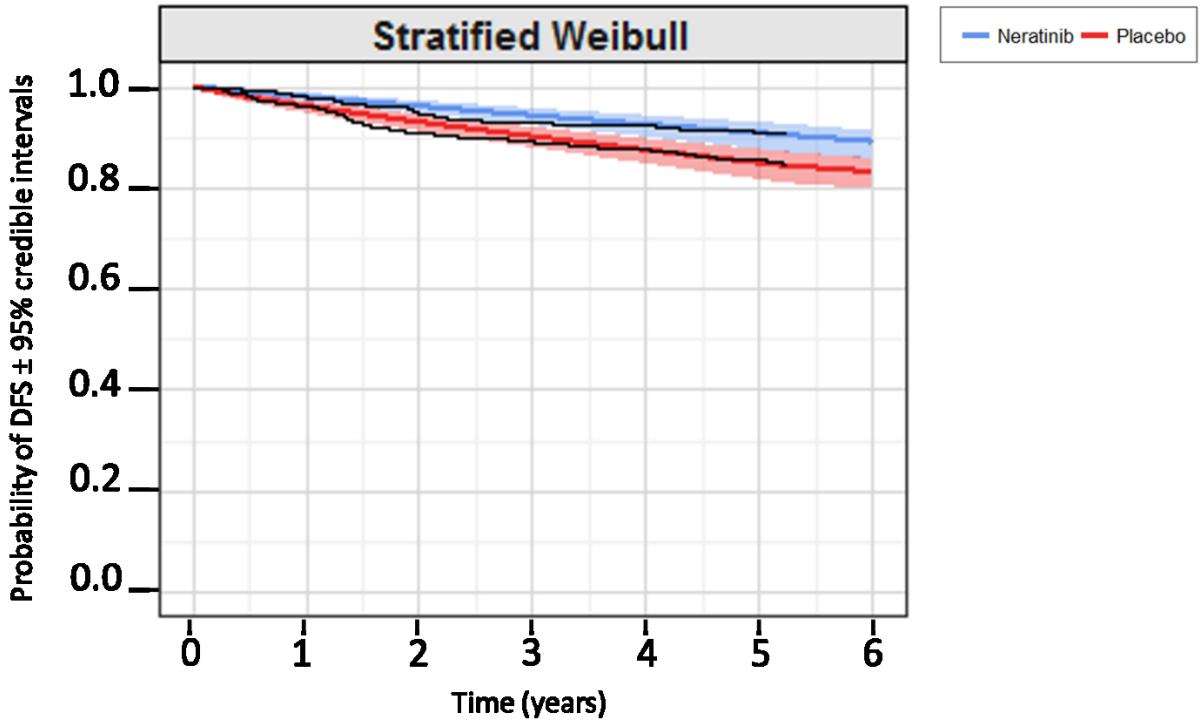
Based on Figure L14A in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.2: Weibull



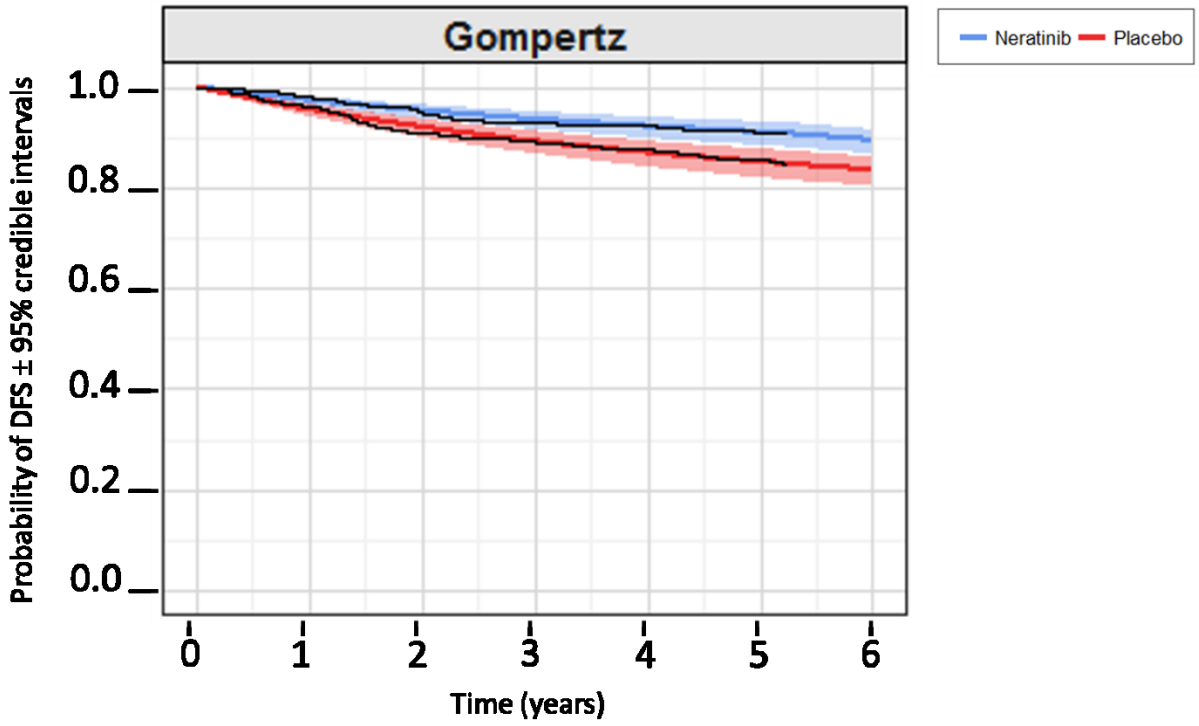
Based on Figure L14B in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.3: Stratified Weibull



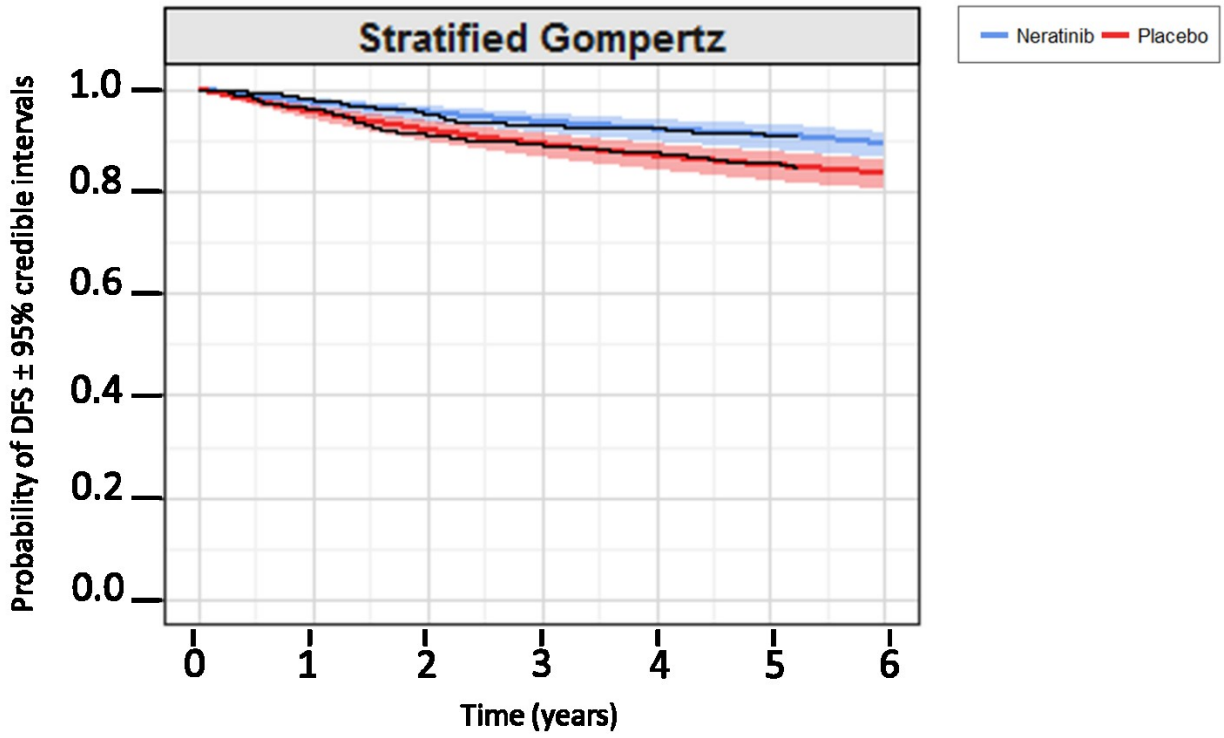
Based on Figure L14C in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.4: Gompertz



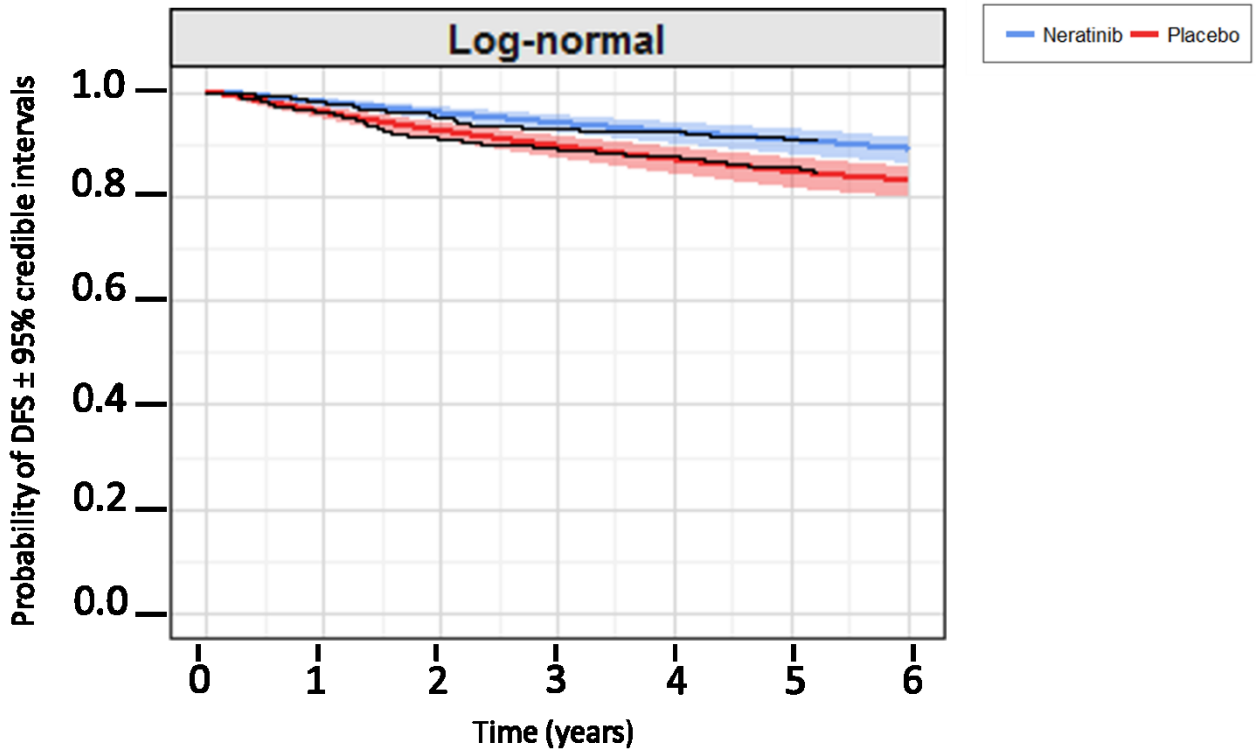
Based on Figure L14D in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.5: Stratified Gompertz



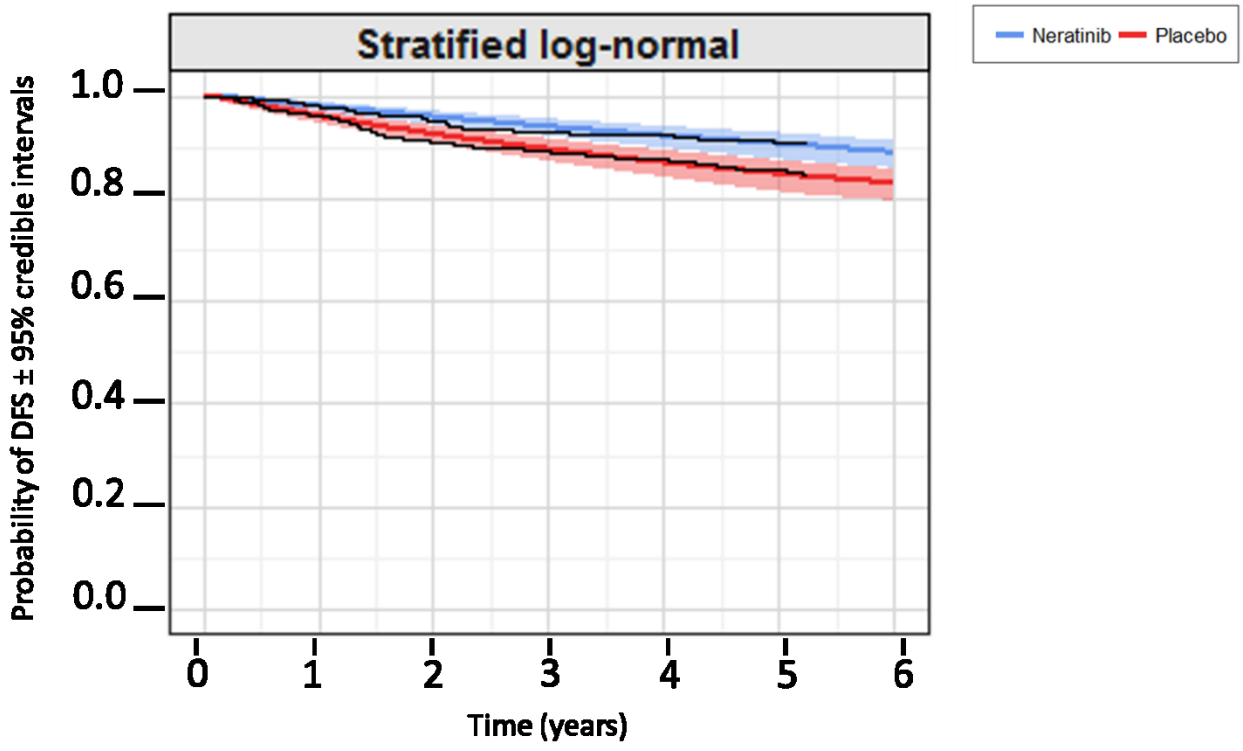
Based on Figure L14E in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.6: Lognormal



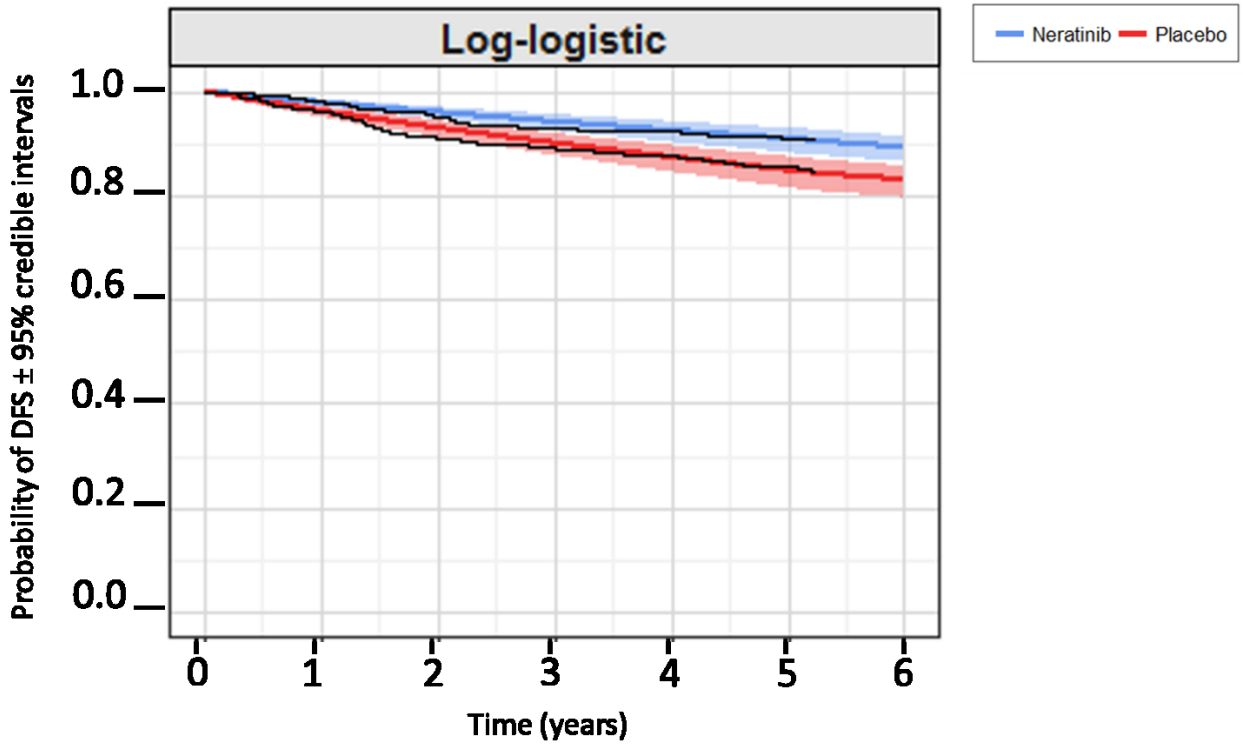
Based on Figure L14F in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.7: Stratified lognormal



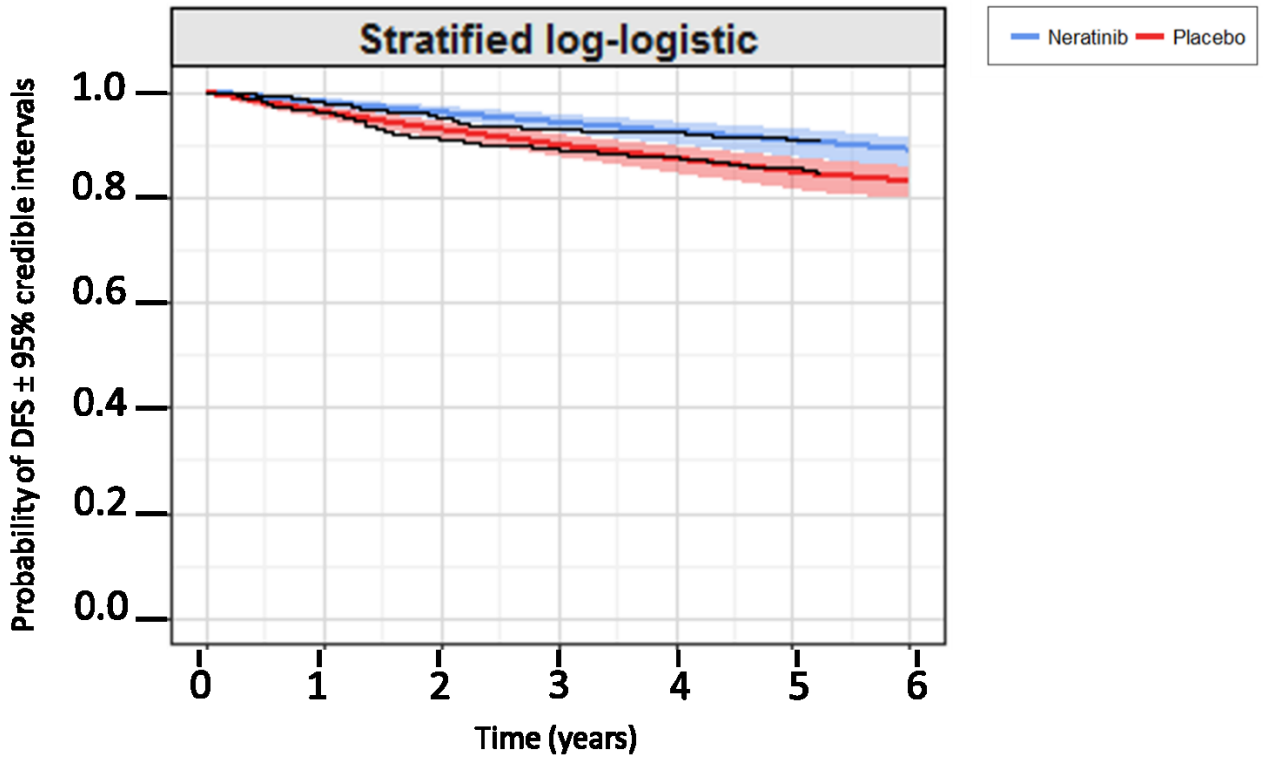
Based on Figure L14G in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.8: Log-logistic



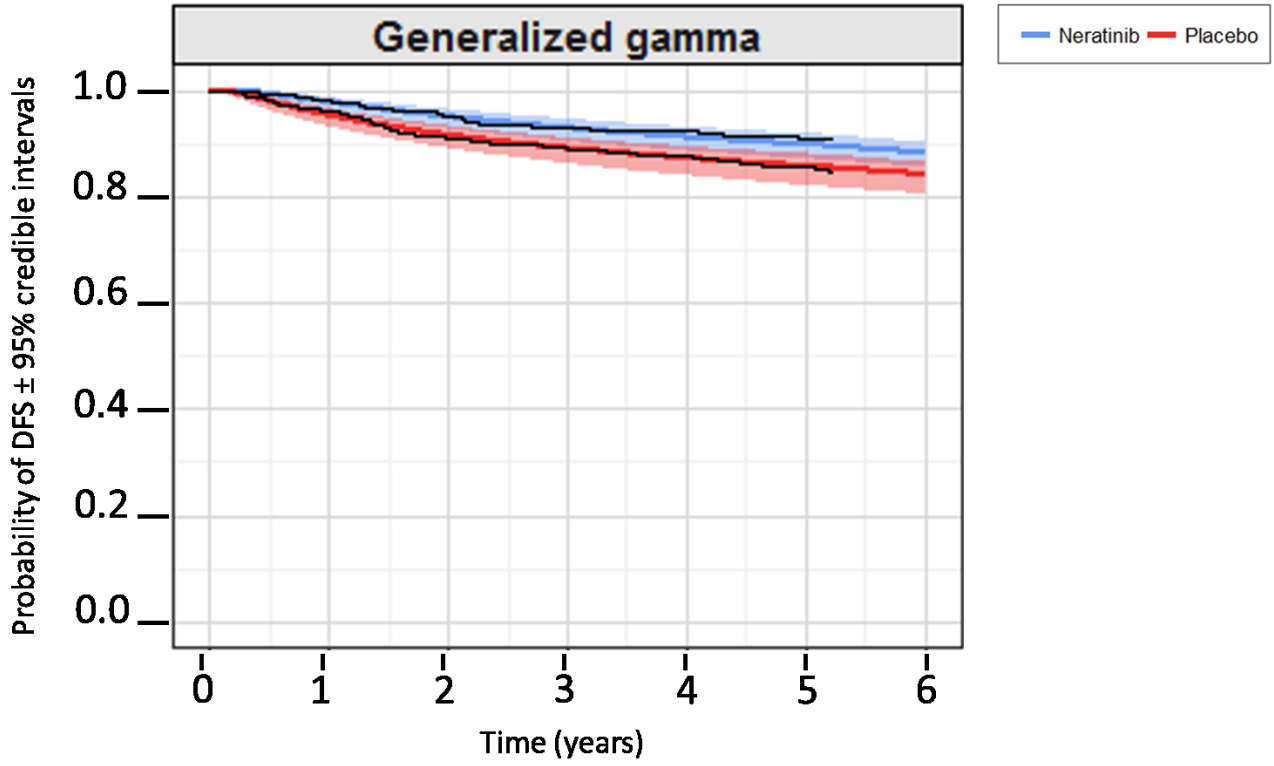
Based on Figure L14H in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.9: Stratified log-logistic



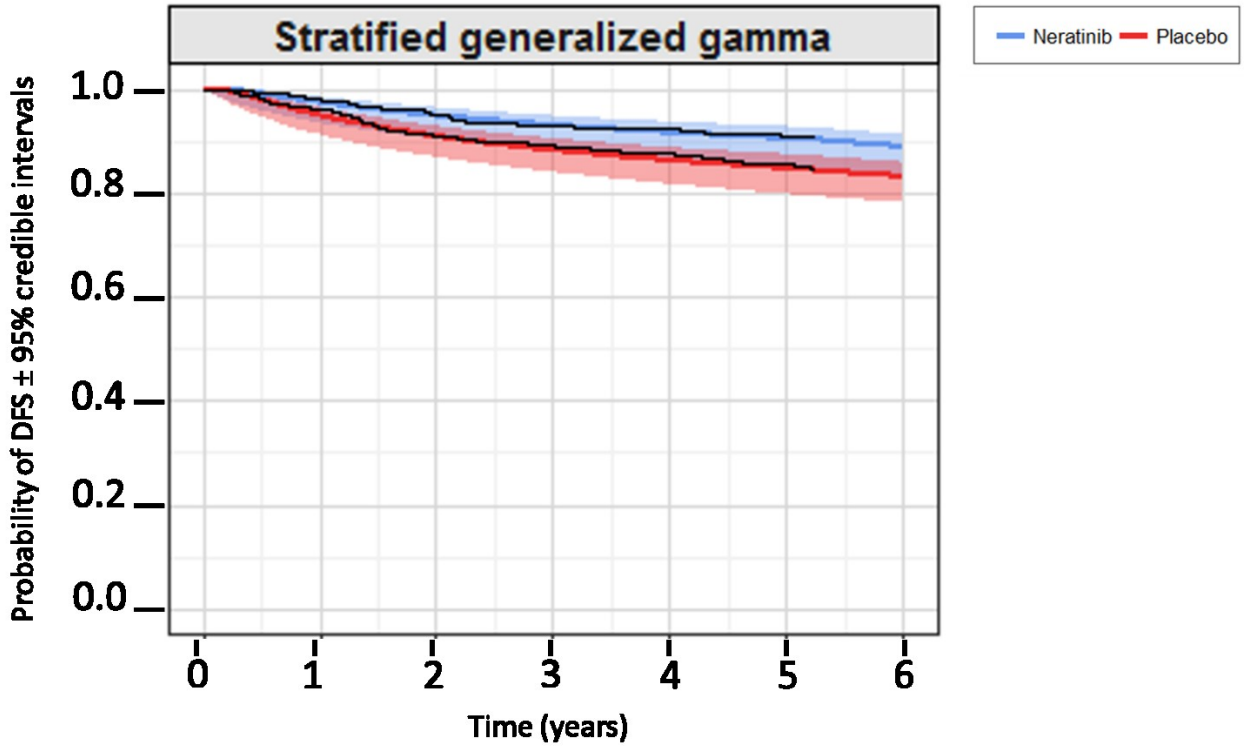
Based on Figure L14I in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.10: Generalised gamma



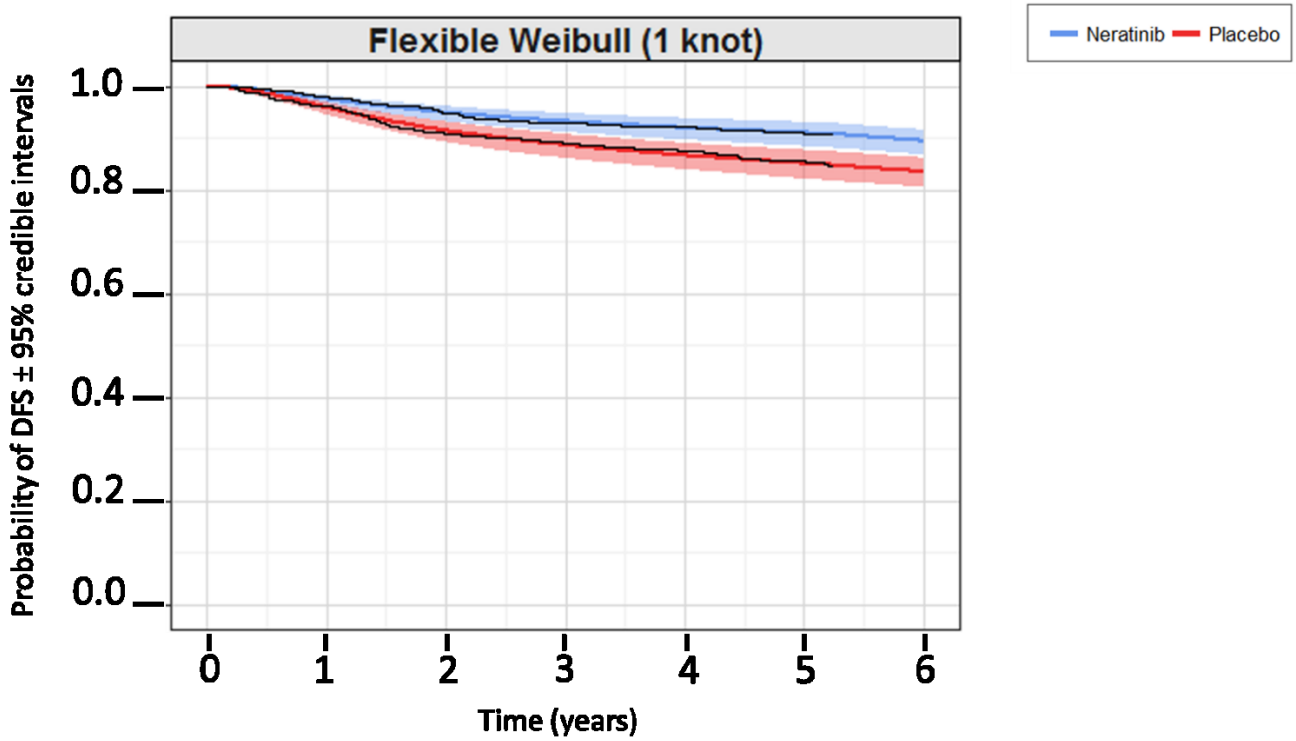
Based on Figure L14J in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.11: Stratified generalised gamma



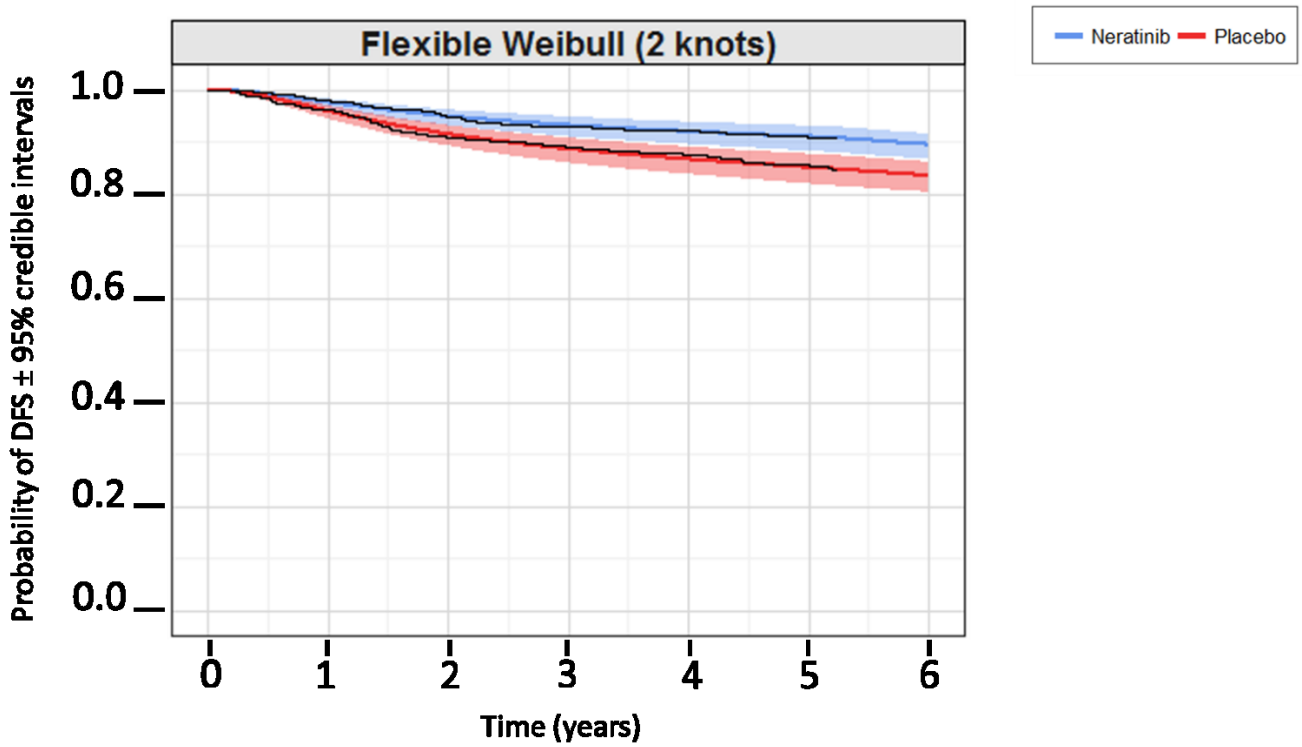
Based on Figure L14K in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.12: Flexible Weibull (one knot)



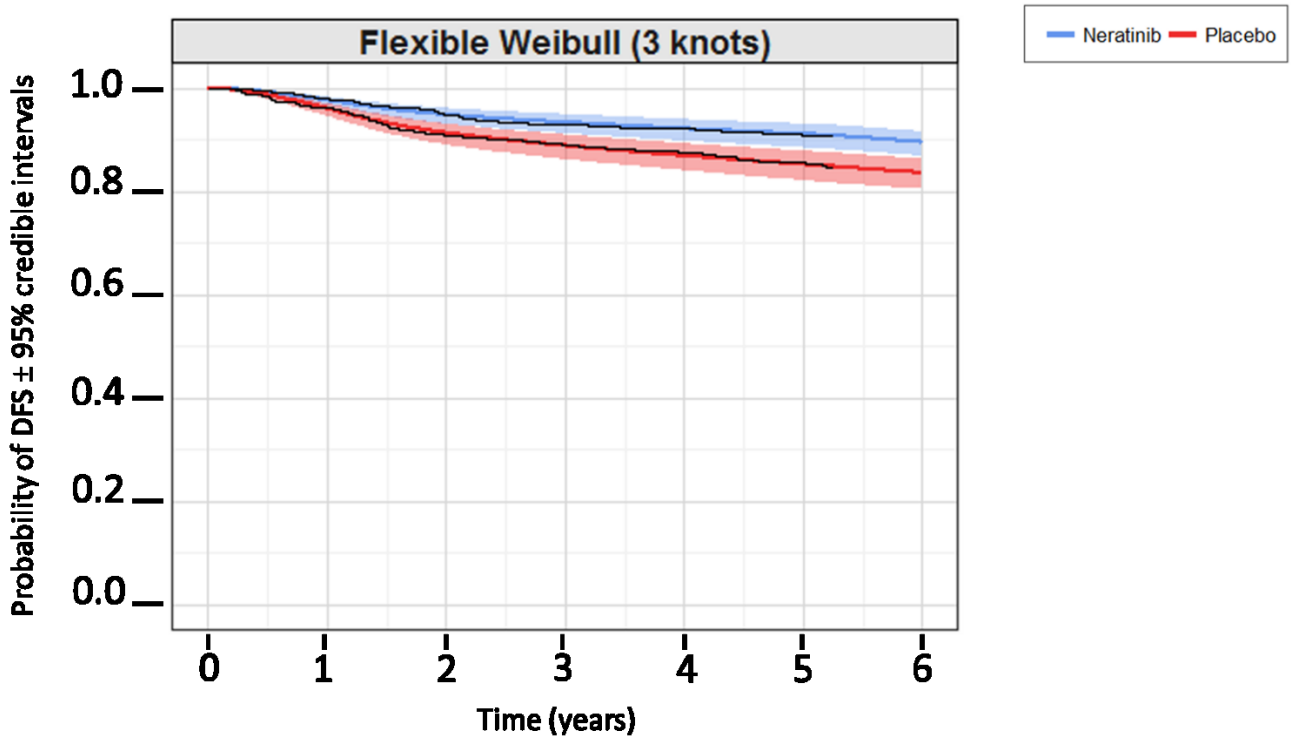
Based on Figure L15A in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.13: Flexible Weibull (two knots)



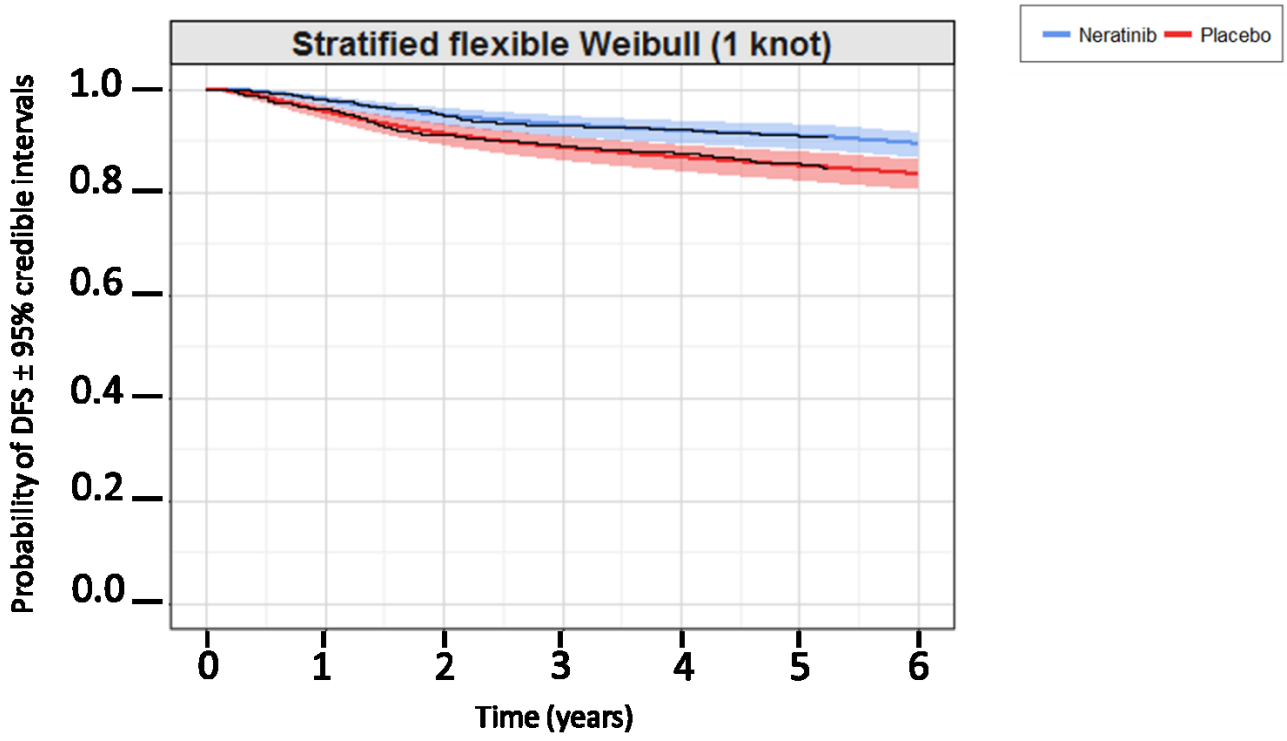
Based on Figure L15B in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.14: Flexible Weibull (two knots)



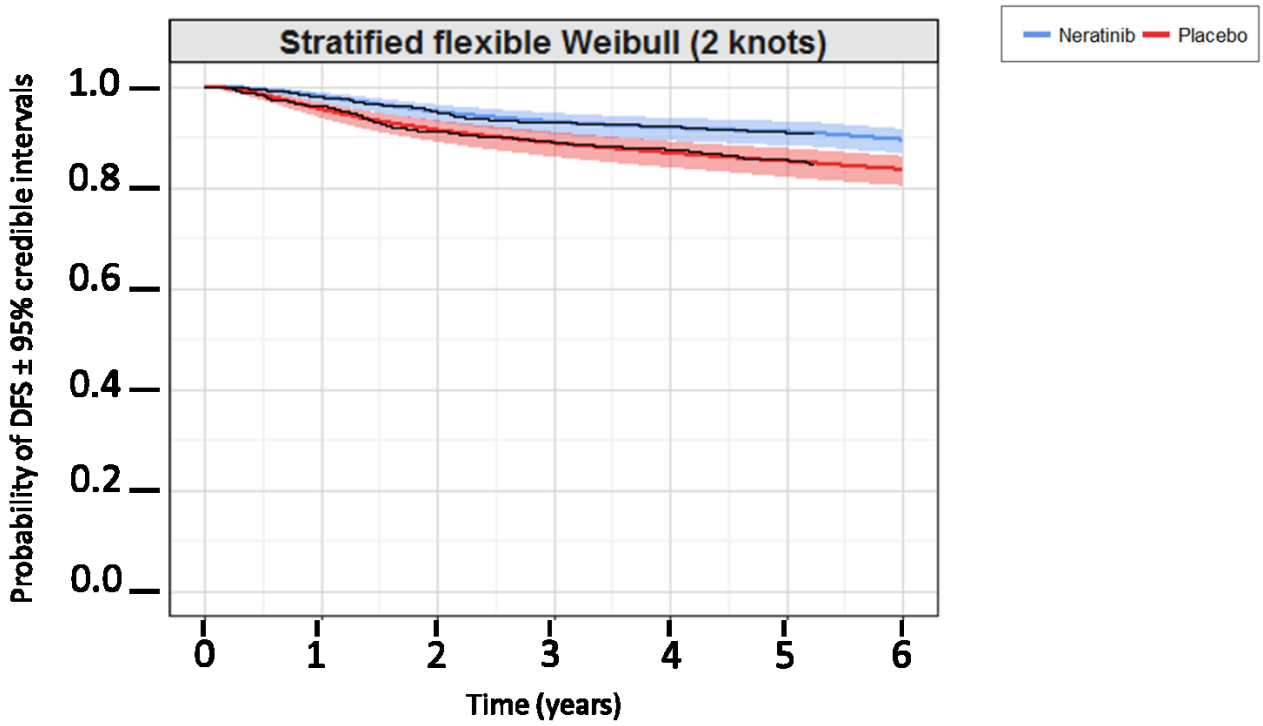
Based on Figure L15C in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.15: Stratified flexible Weibull (one knot)



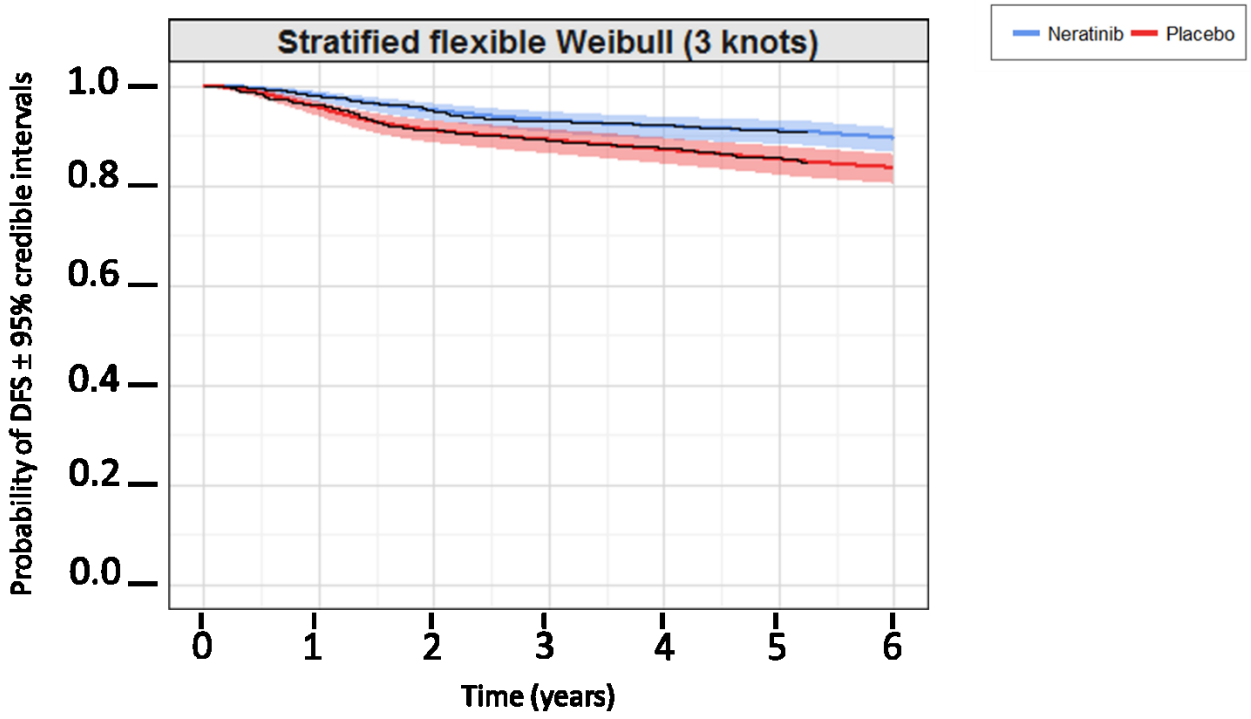
Based on Figure L15D in company response to clarification questions[16]
DFS = Disease free survival

Figure A2.16: Stratified flexible Weibull (two knots)



Based on Figure L15E in company response to clarification questions[16]
DFS = Disease free survival

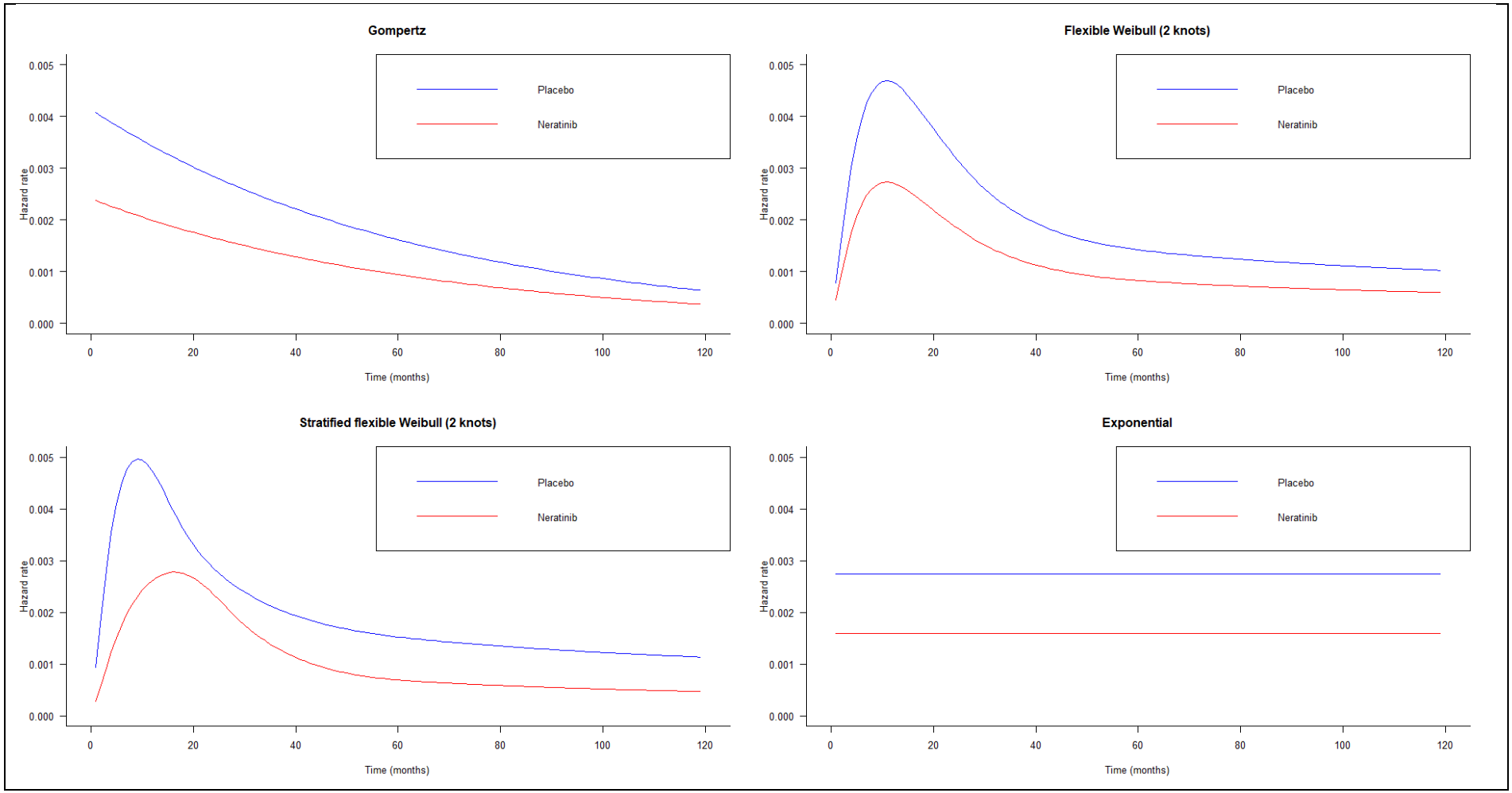
Figure A2.17: Stratified flexible Weibull (three knots)

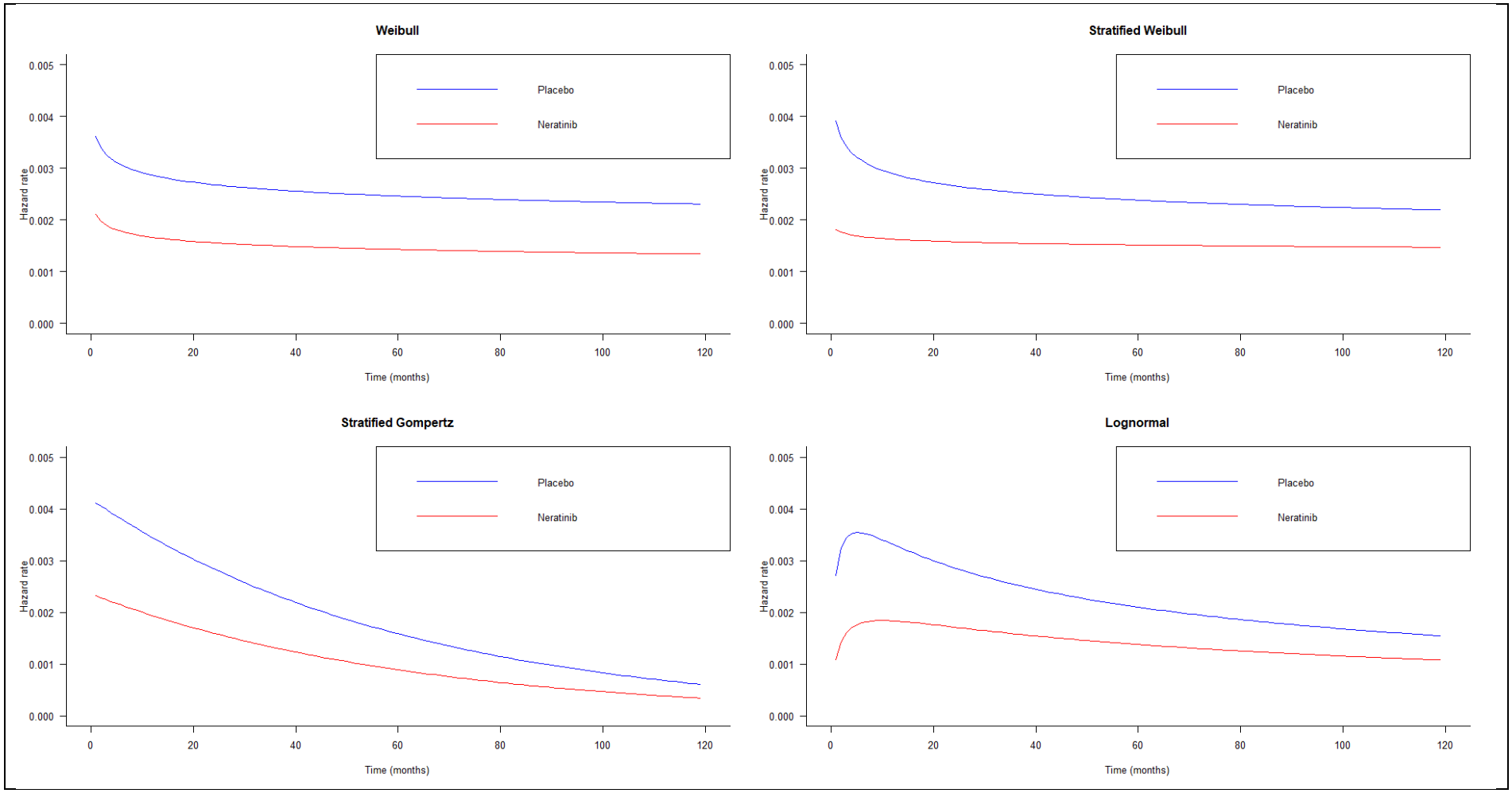


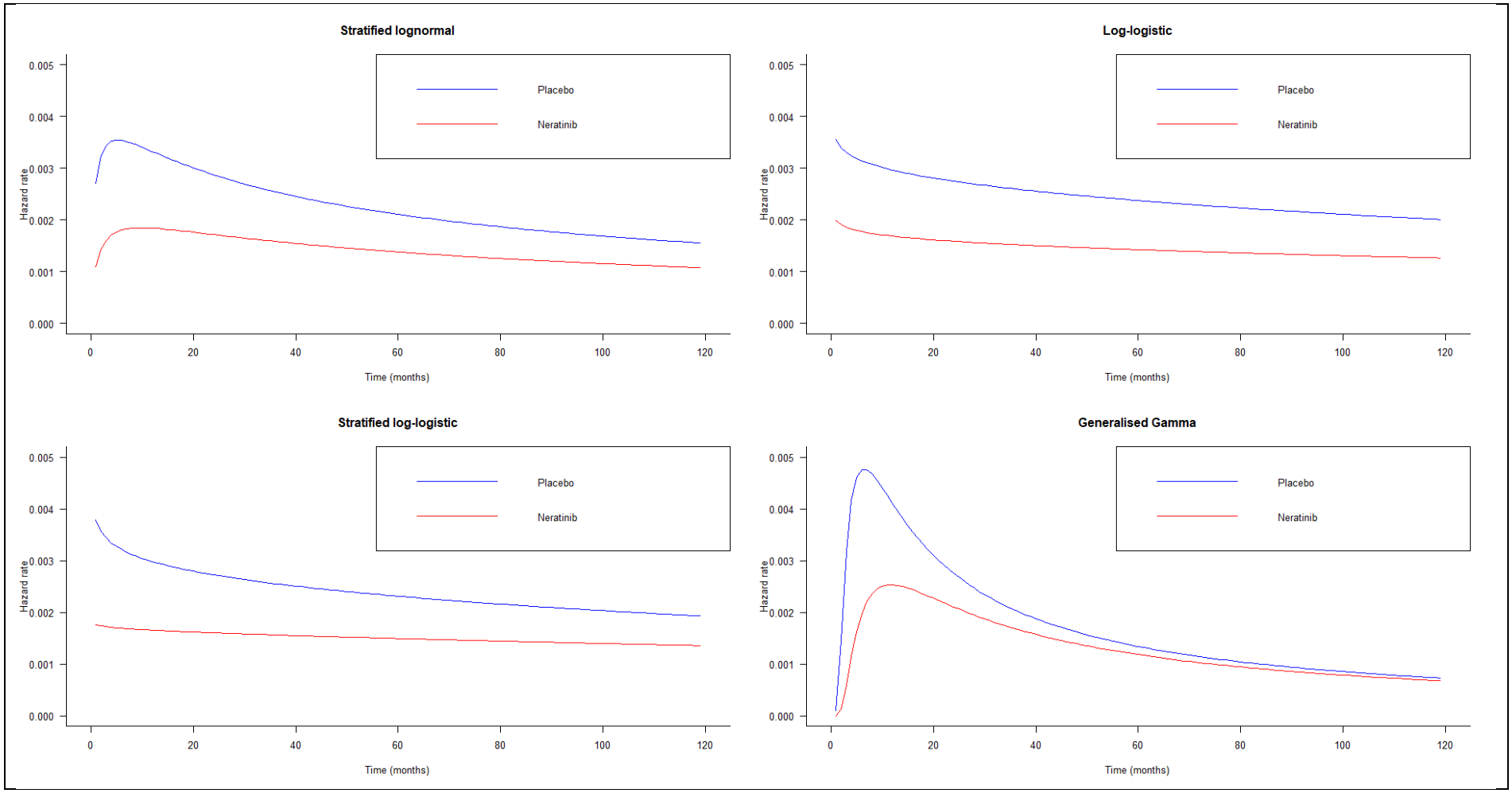
Based on Figure L15F in company response to clarification questions[16]
DFS = Disease free survival

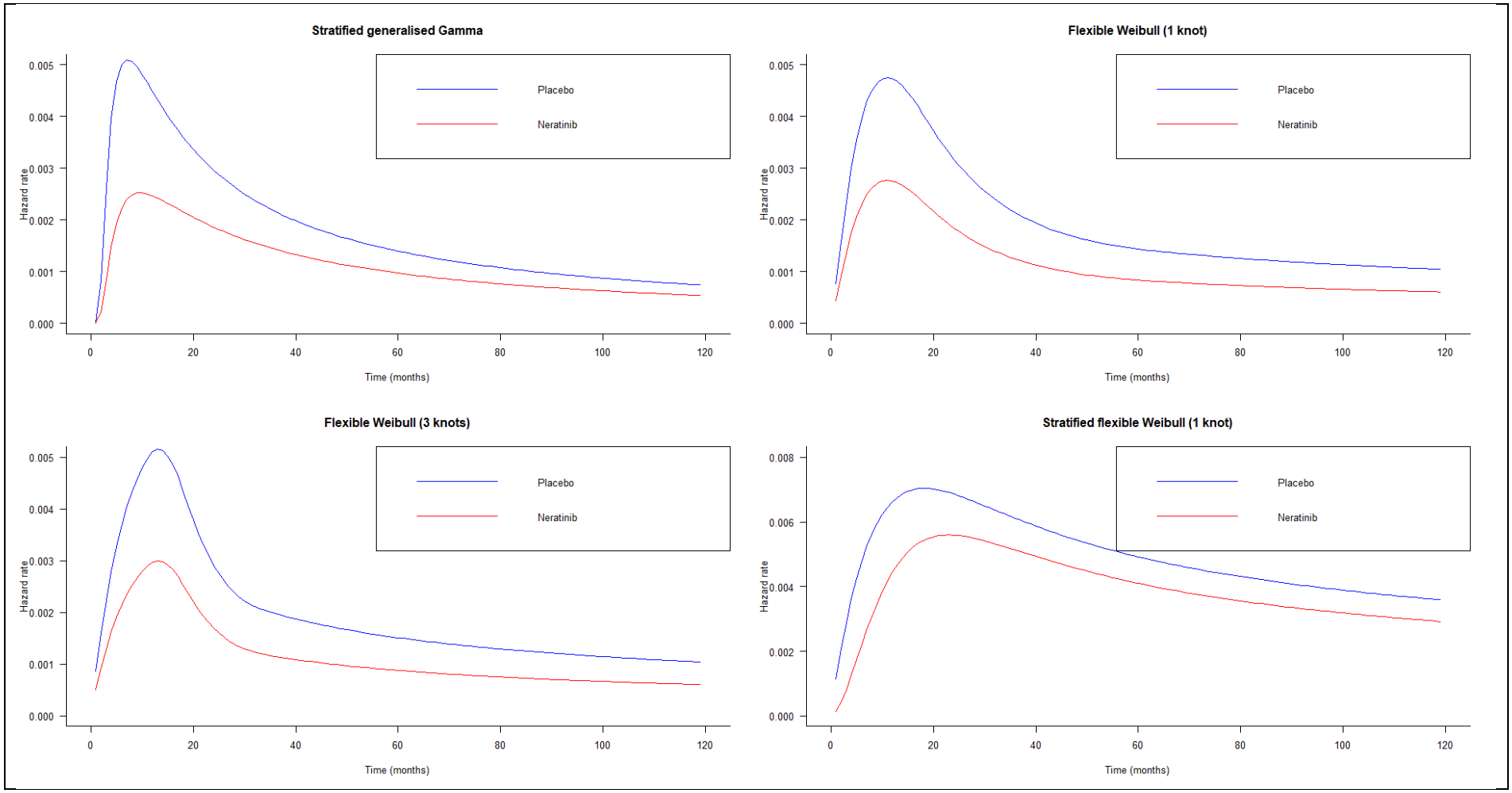
Appendix 3: Hazard rate functions and hazard ratio for survival models fitted to the disease-free survival data from the ExteNET trial data: trastuzumab therapy completed within the past 12 months: HR+

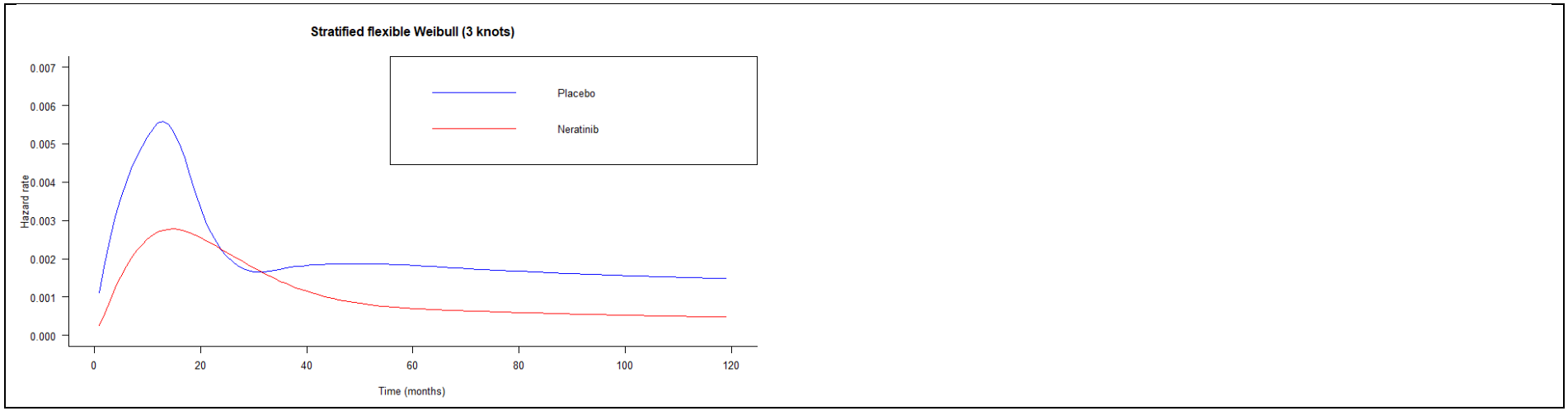
Figure A3.1: Hazard rate functions




Weibull
Placebo
Neratinib
Hazard rate
0.000
0.001
0.002
0.003
0.004
0.005
0
20
40
60
80
100
120
Time (months)
Stratified Weibull
Placebo
Neratinib
Hazard rate
Time (months)
Stratified Gompertz
Placebo
Neratinib
Hazard rate
Time (months)
Lognormal
Placebo
Neratinib
Hazard rate
Time (months)


Stratified lognormal
Log-logistic
Stratified log-logistic
Generalised Gamma
Placebo
Neratinib
Hazard rate
Time (months)
0.000
0.001
0.002
0.003
0.004
0.005
0
20
40
60
80
100
120

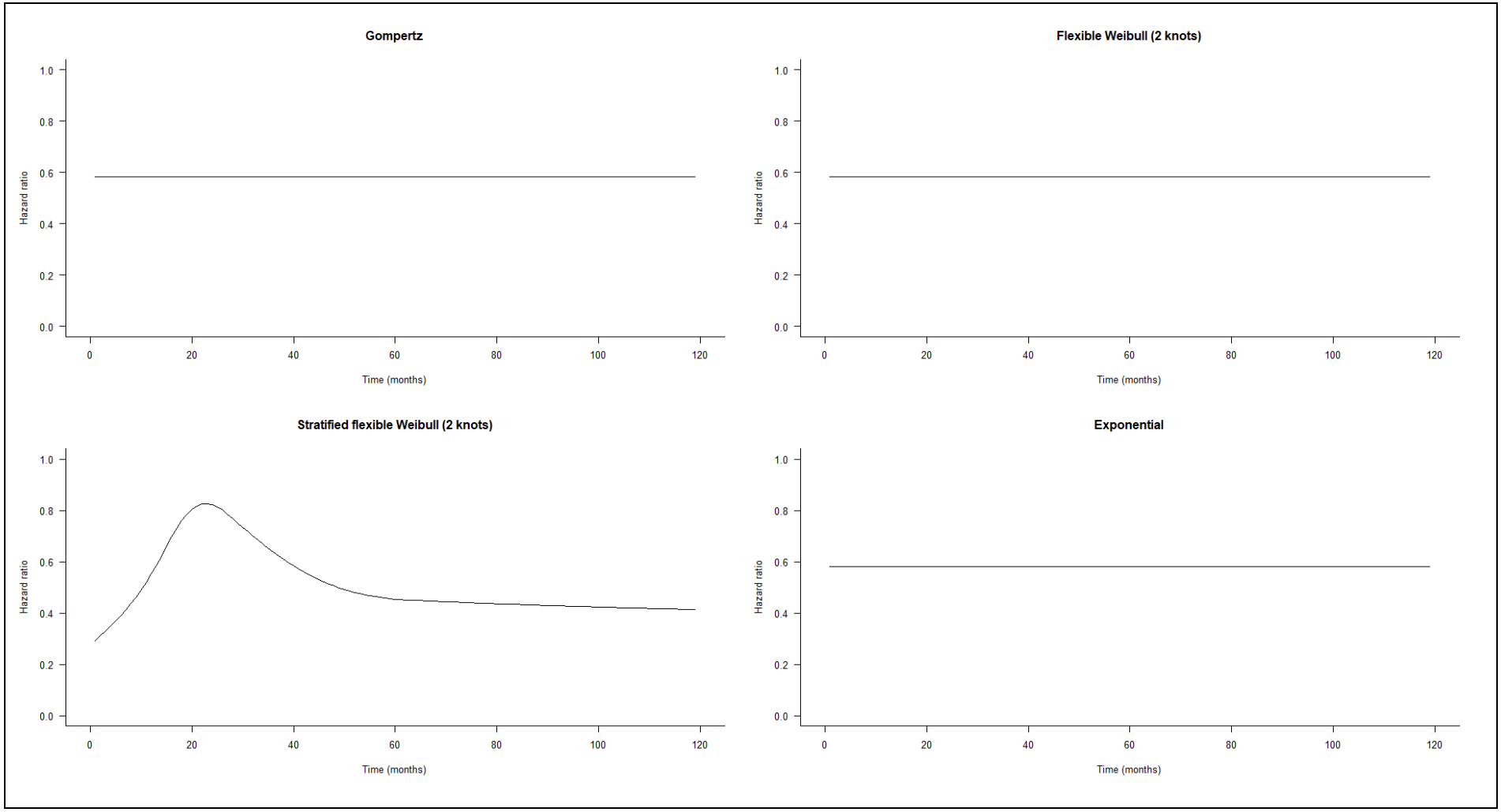

Stratified generalised Gamma
Flexible Weibull (1 knot)
Flexible Weibull (3 knots)
Stratified flexible Weibull (1 knot)
Placebo
Neratinib
Hazard rate
Time (months)
0.000
0.001
0.002
0.003
0.004
0.005
0.006
0.008
0
20
40
60
80
100
120

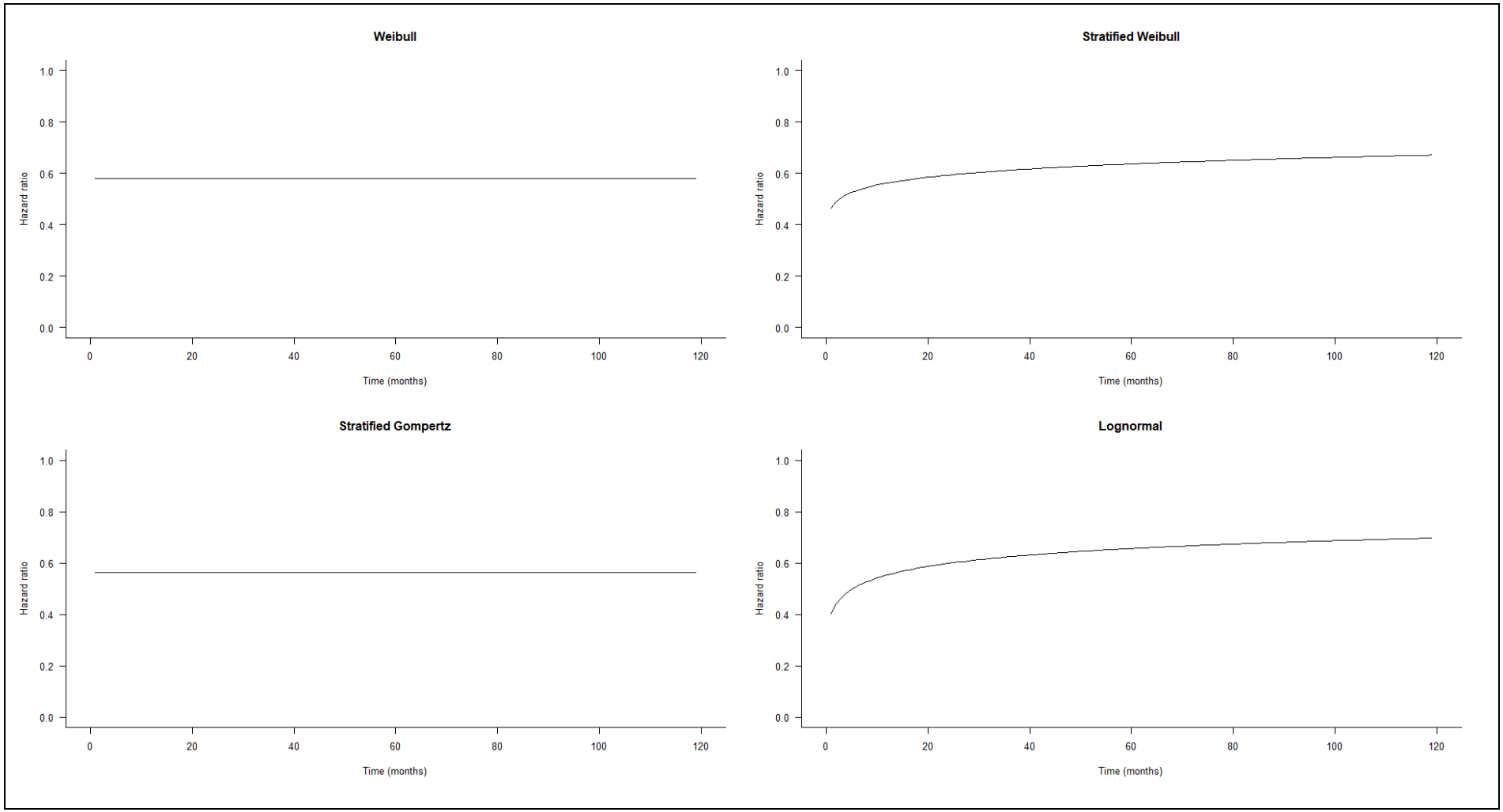


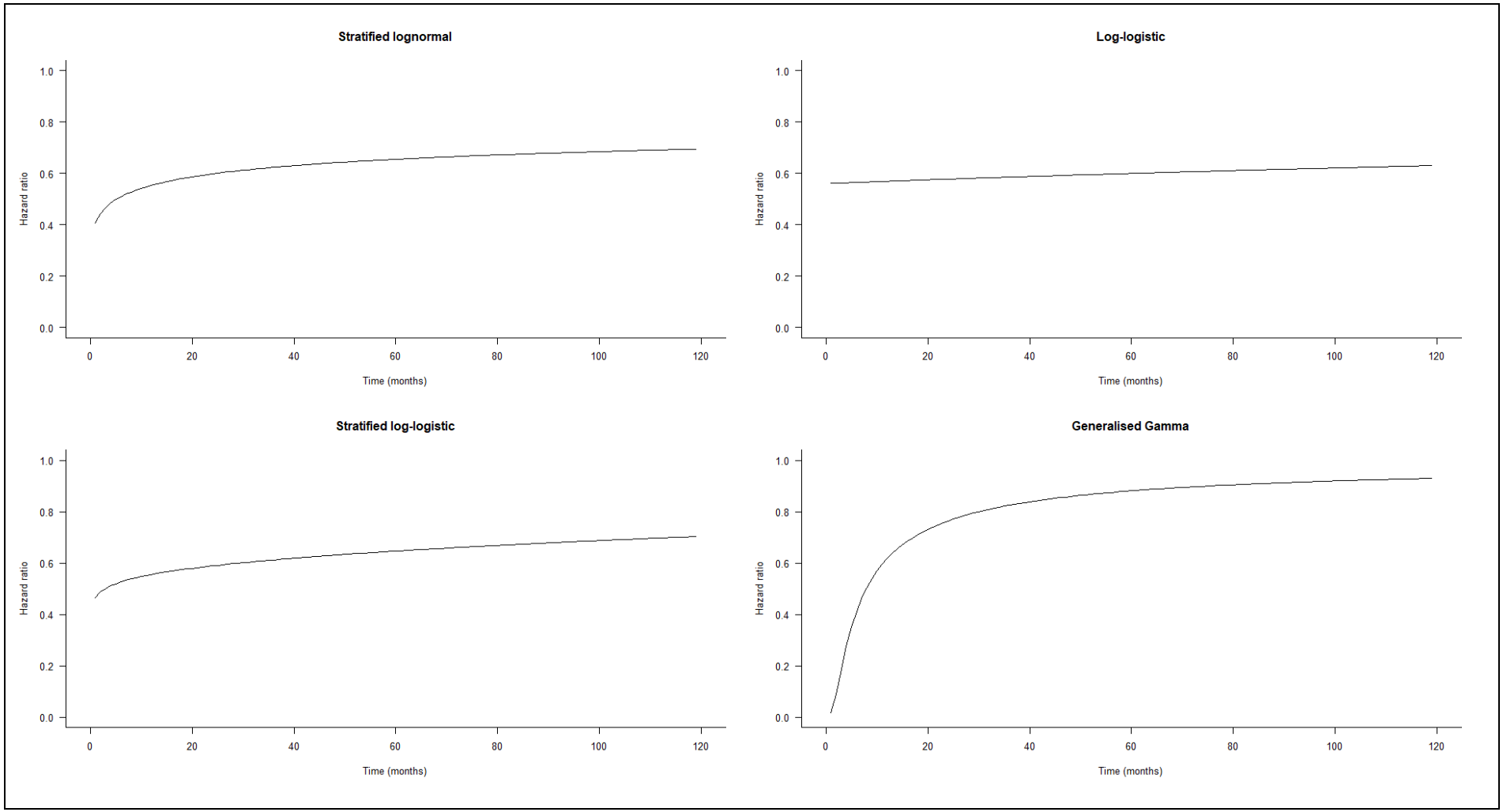
Source: ERG, based on data from the electronic model

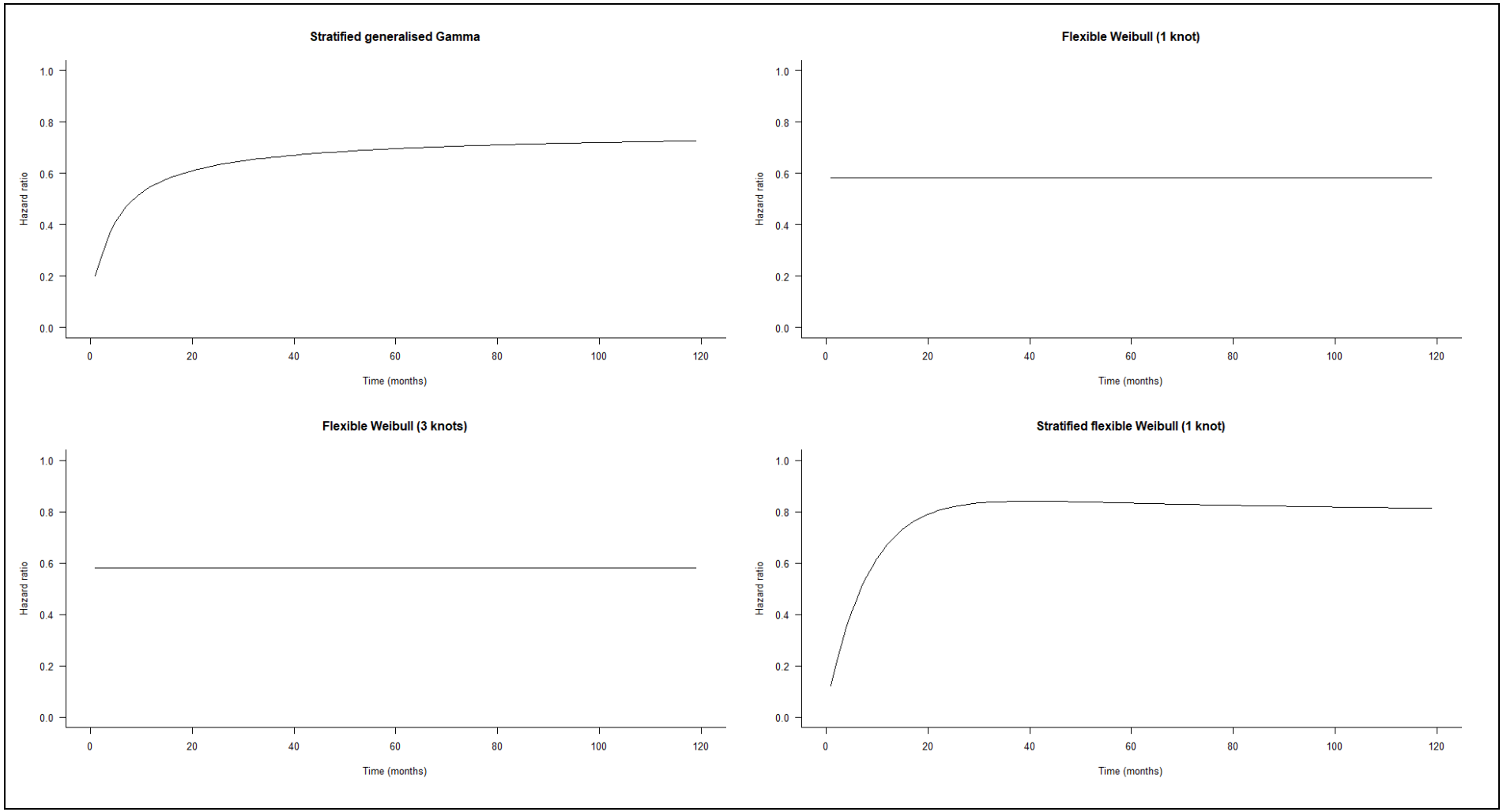
HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive

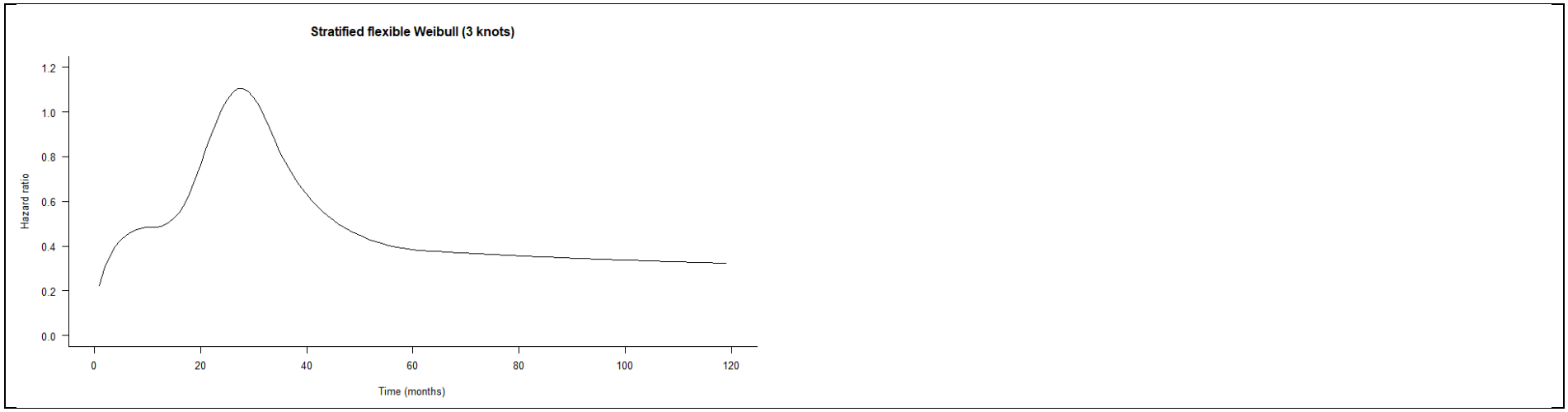
Figure A3.2: Hazard ratio




Weibull
Hazard ratio
Time (months)
Stratified Weibull
Hazard ratio
Time (months)
Stratified Gompertz
Hazard ratio
Time (months)
Lognormal
Hazard ratio
Time (months)


Stratified lognormal
Hazard ratio
Time (months)
Log-logistic
Hazard ratio
Time (months)
Stratified log-logistic
Hazard ratio
Time (months)
Generalised Gamma
Hazard ratio
Time (months)


Stratified generalised Gamma
Hazard ratio
Time (months)
Flexible Weibull (1 knot)
Hazard ratio
Time (months)
Flexible Weibull (3 knots)
Hazard ratio
Time (months)
Stratified flexible Weibull (1 knot)
Hazard ratio
Time (months)



Source: ERG, based on data from the electronic model

HR+ = hormone receptor-positive (oestrogen receptor-positive and/or progesterone receptor-positive

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Neratinib for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab [ID981]

You are asked to check the ERG report from Kleijnen Systematic Reviews (KSR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Thursday 18 April 2019** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Description of DATECAN definition of iDFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11 and page 26, definition of iDFS citing DATECAN, refers to the original article and not the addendum. In the addendum, Table 2 has been corrected to show that iDFS should not include DCIS (ipsilateral or contralateral). Furthermore, it is important to note that the ExteNET trial was initiated in 2009 with final protocol amendments made in 2014, thus the definition of iDFS included in the study pre-dates the publication of the DATECAN definition.	Suggest the addendum is referred to and cited: Gourgou-Bourgade S, Cameron D, Poortmans P, Asselain B, Azria D, Cardoso F, et al. Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials). Ann Oncol. 2015 Dec;26(12):2505-6 Rather than the original article: Gourgou-Bourgade S, et al. Ann Oncol. 2015 May;26(5):873-9. • Point 5 in the list of events included in iDFS on page 11 should be removed. • Two rows in Table 3.2 that refer to DCIS should be removed • Reference should be updated Wording around the ExteNET trial not using the standard definition of iDFS should be amended to make clear that the study predated that definition. "It should be noted that the definition the company used for iDFS was narrower than the standard definition." Should be change to "It should be noted that the definition the company used for iDFS pre-dated, and was narrower than, the now standard definition"	DCIS is not considered invasive and should not therefore be included in the definition of iDFS – as is seen in the amendment to the original article. Furthermore, the standard definition of iDFS was not published when ExteNET commenced.	The ERG report was amended accordingly.

Issue 2 Inaccurate reporting of data in the company submission.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13, Table 1.2 states in the footnote: "a None classified as grade 4 [according to Table 22 of the CS, however, according to Table 25 (reproduced below), there was one grade 4 event in the ExteNET trial]"	Table 25 in the CS presents data for the wider ITT safety population and includes the 1 grade 4 event. Table 22 in the CS presents data for the label population and correctly states that there were zero grade 4 events. This can most easily be seen by comparing Table 21 and Table 22 in the CS which present grade 1-4 TEAEs occurring in ≥ 10% of the safety population and label populations respectively. Amend footnote to read only "[a] None classified as grade 4"	Currently wording in the ERG report misrepresents the information available.	The ERG report was amended accordingly.

Issue 3 Inaccurate reporting of data in the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 in section 1.2 and page 46, Section 4.2.4 state incorrect values "in the ExteNET trial 90% of the participants in the neratinib arm took some anti-diarrhoeal medication (compared to 40% in the control arm)."	The correct values reported in the response to clarification questions are 89.6% and 41.7%	Values presented are not accurate and include a rounding error	The ERG report was amended accordingly.

Issue 4 Contradictory Statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, Section 1.3 states: "Regarding the treatment effect, the company assumed for the base-case analysis that the treatment effect observed at the end of the five-year follow-up would	The text should be changed to read as follows, "Regarding the treatment effect, the company assumed for the base-case analysis that the	The current wording misrepresents the waning of the	The ERG agrees with the company and the sentence

be maintained without further adjustments beyond the trial time horizon. The ERG does not agree with this choice and considers that a waning in the treatment effect is more plausible." These statements misrepresent how the treatment effect was modelled so that the reader is misled to believe that the treatment effect was kept constant indefinably. The ERG has stated this in their report, Page 77, Section 5.2.6 states: "Then, from month 130 to month 176 (during 3.83 years), the HR increases (on average 0.009 per year) until it becomes one. So implicitly, there is a waning of the treatment effect starting at month 130. In total, 14.6 years of neratinib treatment effect are assumed for the base-case (starting from baseline until the time point where placebo and general population mortality hazards are the same)." This better represents the way treatment effect was modelled and thus changes to the text on page 14 should be included to reflect this.	treatment effect observed at the end of the five-year follow-up was maintained until the patients had equal risk of an iDFS event as the general population. This implicitly means that there is a waning of the treatment effect starting at month 130 with a taper of effect over the next 3.83 years (month 176) at which point no further treatment effect is included in the model. The ERG does not agree with this choice and considers that a more rapid waning in the treatment effect is more plausible."	treatment effect in the model analysis.	has been amended as suggested.

Issue 5 Inaccurate reporting of the data available and used in PDRS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, section 1.3 states. "It is unclear whether post-distant recurrence survival (PDRS) analyses are based on the ITT or the label population." This is further states in section 5.2.6, page 79 "However, it is unclear whether PDRS analyses are based on the ITT or the label population.	The ERG statement should be amended to correctly reflect that the CS states the data are for the label population and the following statement in the text adjusted accordingly to reflect this change.	Currently wording in the ERG report misrepresents the information available to the ERG in the CS.	The ERG agrees with the company and this issue has been amended. Note however that the ERG still finds the labelling confusing and inconsistent

Figures 34 to 36 of the CS, provide contradictory information about this." Page 81 also states "It is unclear whether PDRS analyses are based on the ITT or the label population." However, in the company submission, section B.3.3.5.1 Distant recurrence survival, clearly states that blinded label data are used. The chart titles state the population is the label population: e.g. Figure 35 "Kaplan-Meier plot of analysis of overall survival postdistant recurrence for HR+ patients who completed trastuzumab ≤ 1 year by time of distant recurrence, ITT population" The label population is a subset of the ITT population, hence the labelling. Further this was not queried in the clarification questions from the ERG to the company which could easily have clarified this uncertainty.			(Figure 34 is different from Figures 35 and 36).

Issue 6 Inaccurate adjustment to the company model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 1.3, page 15, and again in section 5.2.8, page 86 the ERG state "Since the overall utility of the general population is expected to decrease in time, the ERG considers it plausible to incorporate in the economic analysis the age-based decline in utilities from Janssen and Szende 2014."	The ERG should adjust the utility multiplier to be based on the 55-64 years age group to reflect the modelled patient population. All analyses where this change has been incorporated by the ERG should be rerun to present the corrected ICER.	The error overstates the utility effect associated with increasing age in the model, overstating the effect on QALYs.	The ERG would like to thank the company for detecting this implementation error. The reference multiplier should be based on the 55-64 age range indeed.

This has been incorrectly incorporated by the ERG with the multiplier based on the 18-24 age range when it should be based on the 55-64 age range to reflect the starting utility of the modelled patient population.	Proposed corrections have been included in updated model on the Utility sheet.		However, the correction proposed by the company was also incorrect since the reference age range should be kept fixed for all the other age ranges. This has been corrected by the ERG. All analyses where this change was incorporated by the ERG were re-run and corrected ICERs were presented.

Issue 7 Misrepresentation of the model development process

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 1.6.1, page 19, the ERG state: "The model developed by the company was based on the model developed for the appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer." and section 5.1.4 page 53 "The current model was largely based on the model developed for the appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer" A similar statement is also repeated in Table 5.1 in section 5.2. This is not based on any statement made in the company submission and misrepresents the model development process and understates the differences between the two modelling approaches. Although some inputs and assumptions are based on the pertuzumab model, the model presented in the CS is de novo. The similarities in model	A change to the wording used by the ERG should be made in all instances where this is stated to clarify that while the model shares similarities with that of pertuzumab for adjuvant treatment of early HER2+ breast cancer, the model is not based on the pertuzumab model as this could imply that the structure, inputs and analyses are the same, which they evidently are not. This will ensure the report is consistent in approach; more appropriate wording is used on page 14 or page 59 of the ERG report: "The structure of the conceptual model for this submission was similar to that taken in the NICE technology appraisal of pertuzumab for adjuvant treatment of early HER2+ breast cancer (TA569)" or "Given the similar clinical pathway for the patient populations in TA569 and ExteNET, the model used in the company submission for TA569, as well as the input provided by the ERG and the	Currently wording in the ERG report misrepresents the information available.	The ERG agrees with the company and the sentence has been amended as suggested.

structure are driven by the similarity of the population and data challenges faced in the indication. However, the pertuzumab model was not the basis for the company model.	committee, were considered by the company to develop the current model"		

Issue 8 Inaccurate reporting of the company utility analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15, Section 1.3 and Page 20, Section 1.6.2 state "Despite the ERG's concerns regarding the utilities (estimates based on incomplete dataset, appropriateness of regression models used and mixing data sources to estimate utility)" This is inaccurate as the company did not mix data sources to estimate utility and all of the company data analysis are based on the ExteNET study. Utility estimates from a range of sources were used for the health states which could not be populated from the analysis of the trial data.	The ERG report wording should be clarified to state that data sources were not mixed to estimate utility.	Currently wording in the ERG report misrepresents the information available.	The ERG agrees with the company and the sentence has been amended accordingly.

Issue 9 Incorrect data values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 39, section 4.2.2 has an incorrect value, the reported value 660 for the number of patients in the label population in the neratinib arm. This should be 670 so as the two arms sum to the total (670+664 =1,334). The correct values are in Table 4.7 on page 40.	The value should be corrected from 660 to 670	The current value is incorrect	Typographical error has been corrected.

Issue 10 Incorrect data values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 40, section 4.2.2 Table 4.7 contains an error: the values in the "T stage" section of the table categorised as 'missing' for the label population are located in the wrong row, these should be in the 'unknown' row.	The values in the 'missing' and 'unknown' rows for the label population in the 'T stage' section should be swapped. Unknown 250 (18%) 288 (20%) 121 (18.1)~~0~~ 140 (21.1)~~0~~ Missing 1 (<1%) 1 (<1%) ~~121~~ (~~18.1~~)0 ~~140~~ (~~21.1~~)0	The current table is incorrect	The ERG report was amended accordingly.

Issue 11 Data incorrectly described as not being from the label population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 46, section 4.2.3, the ERG state "Figures 4.1 and 4.2 present the two-year and the five-year DFS in HR+ participants of the ITT population who had prior adjuvant trastuzumab ≤ 1 year. While similar results were not provided for the label population…" The data in these figures are from the label population as demonstrated by the title "…DFS in HR+ participants of the ITT population who had prior adjuvant trastuzumab ≤ 1 year", the label population being those patients within the ITT population who are HR+ and had prior adjuvant trastuzumab ≤ 1 year. A similar statement is made on page 61, Section 5.2.3	The text in the section should be revised to clarify that the label data had been provided.	Currently wording in the ERG report misrepresents the information available to the ERG in the CS.	The ERG report was amended accordingly.

Issue 12 Incorrect data value

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 46, section 4.2.4 the following text contains an incorrect value; "…and grade 3 was present in 213 (32.4)" This value is a repeat of the value for grade 1-2 diarrhoea from the line above and should be 261 (39.4) as stated in table 4.11 on page 48 of the ERG report (and in Table 22 of the CS).	The value for grade 3 diarrhoea in the neratinib group should be corrected from 213 (32.4) to 261 (39.4)	The current value is incorrect	The ERG report was amended accordingly.

Issue 13 Incorrect data value

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 52 in section 5.1.3 the text states, "The cost effectiveness SLR search strategy resulted in 1,523 unique abstracts" The figure quoted should be 1,532, in line with Appendix G of the CS.	The number of unique abstracts identified should be changed from 1,523 to 1,532	The current value is incorrect	Typographical error has been corrected.

Issue 14 Incorrect characterisation of the modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 5.1, page 54, the ERG refers to the company model as a partitioned survival model. This is incorrect and also contradicts the ERG's assessment of the model elsewhere in the report, such as section 5.2.2. which describes the model in detail.	The text should be amended to correctly describe the modelling approach – a five-health-state Markov model	The current description is incorrect	The ERG agrees with the company and the sentence has been amended as suggested.

Issue 15 Misrepresentation of the available OS clinical data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In table 5.1, page 54, the test states: "In the absence of data on overall survival (OS)…" A similar statement is included in table 5.2, page 57. 'perspective on outcomes' and Section 5.2.2 page 60 and Section 7.4, page 117 and in other sections This incorrectly states the data availability. Blinded OS data are available for the label population and were submitted as part of the CS. This is clear elsewhere in the ERG report, which includes the following in section 4.6, page 49, "The CS did present a Kaplan-Meier curve of blinded OS for the HR+ population (Figure 13; page 64) but this did not contain results for each treatment group."	The text should be changed to provide an accurate representation of the available data submitted in the CS. The ERG report is currently inconsistent but on page 54 and 57 reads as if no OS data were included as part of the CS or modelling. Text should be changed to "in the absence of data on OS, by treatment group" or similar	Currently wording in the ERG report misrepresents the information available.	The ERG agrees with the company and the sentence has been amended as suggested.

Issue 16 Misrepresentation of the company rationale on approach to modelling subsequent therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.2, page 60, The text states "Based on this criticism, the company decided not to model individual lines of therapy for distant recurrence in the neratinib model." This misrepresents the company rationale in this area of the modelling. As explained in the CS: "As neratinib is not approved in metastatic breast cancer, the subsequent treatment will not be influenced by neratinib treatment for early breast cancer; thus, it was seen as unnecessarily complicated to model post-distant	The text should be changed to read as follows, "Based on this criticism, and the fact that neratinib is not approved in metastatic breast cancer and therefore subsequent treatment will not be influenced by neratinib treatment for early breast cancer, the company decided not to model individual lines of therapy for distant recurrence in the neratinib model."	Currently wording in the ERG report misrepresents the information available.	The ERG agrees with the company and the sentence has been amended as suggested.

recurrence survival (PDRS) specifically for each treatment. Rather, subsequent treatment was modelled by including the cost of the different subsequent treatments and using PDRS from the ExteNET trial. The approach taken in the ongoing NICE appraisal of pertuzumab (ID1192), which specifically modelled survival when in distant recurrence based on trial data from subsequent lines of therapy, was also criticised by the ERG for that submission because it produced ill-fitting OS models compared with the OS observed in the pertuzumab clinical trial. Thus, using PDRS from ExteNET was deemed to better represent the expected survival for the patient population."			

Issue 17 Misrepresentation of the data and model limitations in the economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 5.2.3, page 61, the text states: "A subgroup analysis based on the Western European label population would have been of interest since this could have been more representative for the UK population. However, such analysis was not possible with the current version of the economic model." In the clarification questions, the ERG requested clinical outcomes by geography, and these were provided in the company response. The ERG did not request that these were incorporated into the economic model. Thus, this was not a limitation of the economic model, but the analysis requested. The issues associated with the data are covered by the ERG in section 4.1.4 on page 36 (and noted on	The text should be amended to reflect that data limitations prevented the assessment of the UK specific population in ExteNET. Page 61, change "However, such analysis was not possible with the current version of the economic model" to "However, such analysis was not possible with the data requested"	Currently wording in the ERG report misrepresents the information available.	Not a factual error. At the time the ERG asked for clinical outcomes stratified by geographical region, it was impossible to anticipate the differences in effectiveness between different regions that were observed in the response to the clarification questions. For that reason, the ERG did not ask the company to include this option in the electronic model. Therefore, such analysis is not possible in the current version of the model.

page 19) and relate to UK-specific, rather than European data: "There are concerns regarding the representativeness of the neratinib trial to the UK population. As stated by the company in their clarification response to question A11 (regarding further results on the label population of ExteNET), "the number of UK patients is too small to perform an appropriate statistical test", which causes some concern to the ERG. ExteNET included "80 patients at 13 sites in the UK", however, only 41 (19 in the neratinib arm and 22 in the placebo arm) of these were in the label population." Given that the analyses provided show that approximately one third of patients in ExteNET were in the western Europe subgroup and that efficacy is similar between regions we consider that the neratinib trial data are representative of the UK. It is important to note that these subgroup analyses were not powered to show significance – and the confidence intervals are wide for all the geographical subgroups compared with those for all patients in the label population.			

Issue 18 Misrepresentation of company and ERG assessment of evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 5.2.6.1, page 65 the ERG states "The company ignored part of the results provided within the submission, which resulted in a biased assessment. The analysis of the hazard rates and the hazard ratio in	The text should be changed to read as follows, "It is the ERG's opinion that the analysis of the hazard rates and	Currently wording in the ERG report misrepresents the	Not a factual error. Data on iDFS hazard ratio (or hazard rates) over time were presented in the company submission (e.g. Figure 5.4 and 5.5).

Figures 5.4 and 5.5 clearly suggest that the proportional hazard assumption does not hold for iDFS (e.g. the hazard ratio is not constant over time)." The company believes part of this statement is open to interpretation. Not coming to the same conclusion as the ERG after investigating the data presented in the submission is not equal to ignoring the data as the ERG states. The company were aware of all data presented but did not come to the same conclusion as the ERG. Further, the ERG report states that "Figures 5.4 and 5.5 clearly suggest that the proportional hazard assumption does not hold". However, this is not a fact but the ERG's assessment and should be stated as such. The Therneau-Grambsch statistical test, presented in the CS, shows that the proportional hazard assumption can't be rejected and the ERG has not provided further analyses other than their subjective assessment of the plots.	the hazard ratio in Figures 5.4 and 5.5 suggest that the proportional hazard assumption does not hold for iDFS (e.g. the hazard ratio is not constant over time)."	information available.	However, the assessment of these data was not included (hence ignored) in the company submission. Figures 5.4 and 5.5 provide visual evidence that the proportional hazard assumption does not hold, because the hazard ratio is not constant over time. The Therneau-Grambsch statistical test shows that, with the current evidence, the proportional hazard assumption can't be rejected. However a significant or non-significant p-value cannot be used to deny evidence that can be seen (e.g. a non-constant hazard ratio). Therefore, the ERG acknowledged the uncertainty around the proportional hazards assumption and, unlike the company, considered all possibilities. The company is correct in stating that not coming to the same conclusion is not the same as ignoring data. However, the point still stands that, whatever the conclusion of the company regarding the proportional hazards assumption, it was arrived at without including an assessment of the data in Figures 5.4 and 5.5, i.e. these data were ignored.

Issue 19 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
A missing word changes the interpretation of a sentence on page 67 of the ERG report. "For simplicity's sake, HERA data were included in the base-case extrapolation analysis…"	The text should be changed to read as follows,	The current wording is incorrect	The ERG agrees with the company and the sentence has been amended as suggested.

In line with the CS, this should read “HERA data were **not** included”	“For simplicity’s sake, HERA data were not included in the base-case extrapolation analysis…”		

Issue 20 Misrepresentation of statistical testing for extrapolation functions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 5.2.6, page 68 the ERG state: “Note that the company did not provide any assessment of the stratified Gompertz and stratified log normal distributions.” This is incorrect, assessments were provided in the appendices in Table 57, Table 58 and Table 60.	Clarification of the assessments the ERG is referring to can be made, or the statement withdrawn given the assessments of these functions provided in the appendices.	The current wording is incorrect	The ERG agrees with the company and the sentence has been amended as suggested.

Issue 21 Misrepresentation of evidence by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.1 page 78 the ERG states “The analysis of the hazard rates and the hazard ratio in Figures 5.4 and 5.5 clearly indicates a waning of the treatment effect.” As this is the opinion of the ERG it should be worded as such.	The text should be changed to read as follows, “The ERG believes that the analysis of the hazard rates and the hazard ratio in Figures 5.4 and 5.5 indicates a waning of the treatment effect.”	The current ERG report states assumptions and opinions as facts	Not a factual error. See Issue 18.

Issue 22 Error in input of diarrhoea events in model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.7, page 82, Table 5.5. The value for Diarrhoea grade 1/2 without prophylaxis should be 5.2 not 6.5 to be consistent with the approach used with the other parameters using the same data source. This value should have been amended to 5.2 net value of All events (6.5) – Grade 3+ events (1.3). This seems to have been an oversight and has a very minor impact on model results.	Change the value from 6.5 to 5.2	The current value is incorrect	The ERG agrees with the company. The ERG can confirm that the correct value of 5.2 was implemented in the model. The incorrect value in table 5.5 of the ERG report has been updated.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Neratinib for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab [ID981]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm, Monday 17 June 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Pierre Fabre Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: The treatment pathway has changed	
a. Would extended adjuvant therapy with neratinib be considered following a neo/adjuvant therapy with pertuzumab, trastuzumab and chemotherapy?	○ Pertuzumab as a comparator was not specified in the final scope and consequently is outside the scope of this appraisal. ○ However, whilst data are not available to demonstrate the efficacy of neratinib in the extended adjuvant setting of early breast cancer following a treatment regimen that includes pertuzumab, it is important to note that the mechanisms of action of neratinib and pertuzumab are different. Therefore, it could be anticipated that neratinib would show benefit in patients regardless of prior pertuzumab therapy. ○ In HER2+/ hormone receptor-positive (HR+) patients, clinicians need to be able to assess the risk/benefit and prescribe the most efficacious treatment to meet the patients' needs at each stage of the treatment pathway.
b. Is it possible for committee to make a recommendation for neratinib for patients who have received a prior pertuzumab therapy? If so, how could the effectiveness be estimated?	○ There are no data available to demonstrate the efficacy of neratinib in the extended adjuvant setting of early breast cancer following a treatment regimen that includes pertuzumab. ○ The different mechanism of action of neratinib means that the addition of neratinib following any adjuvant therapy with trastuzumab and pertuzumab is likely to provide additional efficacy in the extended adjuvant setting on top of any provided by adjuvant pertuzumab.
c. If neratinib was recommended as an extended adjuvant therapy would this mean that neratinib would be used instead of adjuvant pertuzumab (as recommended in TA569) for people with hormone receptor positive node-positive disease as clinicians would choose not to use adjuvant therapy with pertuzumab in people with node-positive disease because extended adjuvant therapy with oral neratinib would be available?	○ In the event neratinib is recommended as a treatment option, the decision to prescribe neratinib or pertuzumab would (as discussed at the technical engagement meeting) be made by the clinician. This decision would be based on an assessment of the risk/benefit profile of the two medicines along with the patient's individual clinical situation. ○ A naive comparison of invasive disease-free survival (iDFS) rates indicates a higher rate for neratinib compared with pertuzumab. ○ The efficacy benefit of neratinib in patients in the label indication of ExteNET is greater than that seen for pertuzumab in the adjuvant setting in the APHINITY trial:

	○ ExteNET 5-year iDFS rate: 90.8% for neratinib and 85.7% for placebo, equating to an absolute benefit of 5.1% vs. placebo (unstratified hazard ratio, 0.58; 95% confidence interval [CI], 0.41-0.82; two-sided *P* = 0.002) ○ APHINITY 3-year iDFS: 94.1% with pertuzumab and 93.2% with placebo, equating to a 0.9% absolute benefit with pertuzumab (hazard ratio, 0.81; 95% CI, 0.66-1.00; *P* = 0.045). (See company submission Section A.7.1.) ○ Therefore, clinicians may choose not to use adjuvant therapy with pertuzumab in patients eligible for neratinib if neratinib becomes available in the extended adjuvant setting.
d. Would some patients with node positive disease prefer an oral treatment, with neratinib, later in the treatment pathway instead of pertuzumab given intravenously in the adjuvant setting?	○ In clinical practice and as discussed at the technical engagement meeting, some patients may prefer an oral treatment, but other factors would also be taken into account by clinicians when deciding on the most appropriate treatment regimen.
• **Issue 2: Invasive disease-free survival definition in ExteNET**	
a. Do you think the trial definition of iDFS that excludes second primary invasive cancer (non-breast cancer) and ductal carcinoma in situ events is suitable for the estimation of overall survival?	○ As discussed at the technical engagement meeting, rates of second primary invasive cancer are low; therefore, this definition of iDFS is still expected to correlate with overall survival (OS). ○ The definition of iDFS used in the ExteNET study was standard when the protocol was developed and based on STEEP criteria (Hudis et al., 2007). The STEEP criteria were followed, with the exception that secondary primary (non-breast cancer) would not be included in the iDFS endpoint. This was requested by both the FDA and EMA when the protocol was reviewed. ○ Finally, an addendum to the DATECAN publication excluded ductal carcinoma in situ from the definition, which is therefore not included in the current DATECAN definition of iDFS (Gourgou-Bourgade et al., 2015).
b. Do you think that many events were missed in the neratinib or placebo arm of ExteNET trial because of the iDFS definition used?	○ No—as stated above in 2a, rates of second primary invasive cancer are low; therefore, the trial definition of iDFS is expected to correlate with OS.
• **Issue 3: Invasive disease-free survival modelling**	
a. Which curves look more plausible in relation to the Kaplan-Meier data from the trial? Is the company's or ERG iDFS modelling more	○ Since both distributions provide a very good fit to the Kaplan-Meier data within the trial period, it is difficult to distinguish between the two within the trial period.

appropriate? The effect of the two approaches on cost-effectiveness estimates is large. From looking at the figure in the Appendix of the technical report, would you be able to say which approach is more plausible?	○ There is no clear evidence that the proportional hazard assumption does not hold, and statistical testing shows that survival analysis is more likely to be proportional hazards than not. ○ Pierre Fabre does agree that, if the proportional hazard assumption does not hold (as assumed by the ERG), the stratified generalised gamma curve provides a good fit to the data. ○ Pierre Fabre is willing to accept the consideration of non-proportional hazards and the stratified generalised gamma curve as a conservative approach. However, we would highlight that there is a high degree of uncertainty around this assumption. ○ The ERG also concluded in their assessment that "there is uncertainty regarding the assumption of proportional hazards for iDFS," and it is Pierre Fabre's view that the combination of the non-proportional hazard and stratified generalised gamma curve is very conservative, having a large impact on the incremental cost-effectiveness ratio (ICER), which should be seen as a representing the high end of the most plausible ICERs.

b. Considering the assumption of general mortality in the model, would you consider that the survival benefit associated with neratinib has been over or underestimated?	○ Pierre Fabre considers that the assumption around general population mortality in the local recurrence health state in the model is appropriate, and neither over- nor under-estimates survival.
	○ Clinical evidence suggests that very few patients die from breast cancer having experienced a local recurrence only—they are most likely to move into the distant recurrence health state first. This is supported by the following:
	  ○ Clinical input during dossier and model development.
	  ○ No patients in ExteNET recorded as dying from breast cancer without first experiencing a distant recurrence.
	  ○ The same approach of assuming general population mortality for patients in the local recurrence health state after 90 days was taken in the recent pertuzumab appraisal (trial death used until 90 days).
	  ○ Non-cancer mortality during the ExteNET trial was lower–not higher–than the UK general population.

Issue 4: Duration and type of treatment effect	
a. Is it plausible to assume the ERG's tapering of treatment effect of 6.4 years starting after the ExteNET trial for neratinib?	○ Pierre Fabre is willing to accept the ERG's assumption of a tapering of treatment effect for neratinib of 6.4 years, starting after the ExteNET trial, and consider this a conservative assumption for the following reasons:

	○ As highlighted by the ERG during the technical engagement meeting, the ERG's preferred survival curve for iDFS implies some waning effect, further reducing the treatment effect over time compared with the company preferred extrapolation. ○ As highlighted by the clinical experts at the technical engagement meeting, patients with HER2+/oestrogen receptor-positive (ER+) tumours tend to experience recurrence later than those with ER– tumours; therefore, a long treatment effect would be expected in the label population for neratinib. ○ As reported in the company submission (Section B.1.3.3.1), in the IBCSG clinical trials, the hazard of recurrence was higher for patients with ER+ disease compared with patients with ER– disease after 5 years (5-10 years: 5.4% vs. 3.3%; 10-15 years: 2.9% vs. 1.3%; 15-20 years: 2.8% vs. 1.2%; and 20-25 years: 1.3% vs. 1.4%; $P < 0.001$; HER2 status unknown). ○ Neratinib's intracellular mode of action simultaneously blocks multiple ErbB receptors and has demonstrated inhibition of bidirectional crosstalk between HER2 and ERs that contributes to drug resistance to both HER2-directed agents and endocrine therapy, something that has not been shown with trastuzumab-based regimens and is likely to increase the treatment effect of neratinib.
b. Should a shorter taper period, as applied in TA569, be considered instead?	○ Based on the aforementioned and points below (as discussed at the technical engagement meeting), Pierre Fabre does not think that a shorter taper period would be justified in this appraisal. ○ Neratinib and pertuzumab have different modes of action; thus, their treatment effect patterns would not necessarily be the same; the numerically better results for neratinib could be seen as supporting this. ○ During the appraisal of pertuzumab, the ERG criticised the company submission because the model could not replicate the long-term treatment effect in HERA. However, the ERG did not acknowledge that the HERA trial had > 50% crossover, which has been reported to significantly impact long-term treatment effect in the trial and result in the appearance of waning (Cameron et al., 2017). ○ In addition, recurrence in patients with HER2+/ER+ tumours tends to be later than those with ER– tumours; therefore, a longer treatment effect would be expected in the label population for neratinib. ○ The ExteNET trial provides an additional year of follow-up (5 years) compared with the clinical data for pertuzumab. As presented in the neratinib company submission (Section B.2.6.1), there is no evidence to suggest the hazard rate would significantly increase towards the end of the ExteNET trial, which contradicts the applicability of a rapid waning of treatment effect for neratinib. On this basis, the rapid waning effect applied in the pertuzumab model should not be applied to the neratinib model.

Issue 5: Treatment duration and dose intensity	
a. How should neratinib dose intensity be modelled? Is using the dose based on the ExteNET trial that did not use prophylaxis for diarrhoea appropriate?	○ Pierre Fabre acknowledges uncertainty around the impact of antidiarrhoeal prophylaxis on dose received and how this will impact on cost. However, our assumption is that, if the dose intensity or duration is increased, the efficacy will also improve, and it would be inappropriate to adjust the costs without also adjusting the efficacy. Any adjustments to both costs and efficacy would add further uncertainty because any adjustment would be based on assumptions. ○ Therefore, the approach that minimises uncertainty is to assume the dose intensity and duration from the ExteNET trial.
b. How should neratinib treatment duration be modelled? Is using the duration based on the ExteNET trial that did not use prophylaxis for diarrhoea appropriate?	○ In line with response to Issue 5a above. ○ In addition, results from ExteNET show that treatment duration impacts treatment effect (Gnant et al., 2018), supporting this assumption.
c. Is the ERG's approach appropriate, or should a different approach be used?	○ Pierre Fabre does not agree with the ERG's approach, and believes it is most appropriate to either (i) use the trial data on dose intensity and duration as presented in the company submission or (ii) make assumptions in terms of both efficacy benefits and cost of increased dose intensity/duration as justified in Issue 5a above.
Issue 6: Utilities used in the model	
a. Is using the ExteNET utility for iDFS of 0.837 for iDFS and remission appropriate, or is a lower utility value for iDFS more appropriate?	○ It is most appropriate to use the ExteNET utilities because these meet the NICE reference case, unlike other published utility values that are either in a different population or not based on the EQ-5D.
b. Is using Lidgren et al., 2007 for the remaining states appropriate? This change has a small effect on cost-effectiveness results	○ For health states for which utilities cannot be derived from the ExteNET trial, the Lidgren et al. (2007) rates are appropriate to use.
Issue 7: Outstanding issues	
a. Are there any issues which are not covered above which are relevant to the appraisal?	As noted in the additional areas of uncertainty in the technical report: • *Page 3 to 4: The clinical trial evidence in ExteNET trial is immature. The final OS analysis is expected in [redacted] for the full trial population and in [redacted] for the label population*.

	○ *The two different dates are due to the fact that the timing of the analysis is event driven. In the full intent-to-treat (ITT) population, this is now expected in* [redacted] *Sufficient events will not have occurred in the HR+, within 1 year of trastuzumab subpopulation (EU indication), to allow meaningful comparison between arms until* [redacted]*, as per the existing protocol.* *Exploratory analysis may be possible, to assess OS events within other patient subgroups (including HR+, within 1 year of trastuzumab).* • *Page 4: Only 80 patients at 13 sites in the UK were recruited in ExteNET, and only 41 (19 in the neratinib arm and 22 in the placebo arm) of these were in the label population (n = 1,334)* ○ It is important to note that, in the EU label analysis, 236 patients (35.2%) in the neratinib arm and 264 (39.8%) in the placebo arm were from the region "Western Europe, Australia and South Africa" and are likely to be similar to the UK population.

References

Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al.; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017 Mar 25;389(10075):1195-205.

Gnant M, Iwata H, Bashford AE, Separovic R, Murias A, Vicente E, et al. Duration of extended adjuvant therapy with neratinib in early-stage HER2+ breast cancer after trastuzumab-based therapy: Exploratory analyses from the phase III ExteNET trial. J Clin Oncol. 2018; 36:15 Suppl, abstract 524.

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Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol. 2007 May 20;25(15):2127-32.

Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. Qual Life Res. 2007 Aug;16(6):1073-81.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient Access Scheme submission

Neratinib (NERLYNX®) for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab [ID981]

Submitted by Pierre Fabre Ltd

20 June 2019

1 Introduction

In acknowledgment of the introduction of the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) the transition arrangements as set out in paragraph 3.28 states that commercial flexibilities analogous to simple confidential and complex published Patient Access Schemes will continue to operate and be available for new products using existing processes and in accordance with existing criteria and terms as set out originally in the 2014 Pharmaceutical Price Regulation Scheme (PPRS), and guidance on the National Institute for Health and Care Excellence (NICE) website. Once NHS England establishes the approach in the commercial framework as referred to in paragraph 3.26 of the VPAS (2019), any new commercial flexibilities analogous to simple confidential and complex published PAS will operate in accordance with the commercial framework.

The PPRS (2014) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2014) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow NICE to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for Patient Access Schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with NHS England, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for companies

This document is the Patient Access Scheme submission template for technology appraisals. If companies want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a technology appraisal, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from NHS England.

The template contains the information NICE requires to assess the impact of a Patient Access Scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Company evidence submission template' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal April 2018. The 'User guide for company evidence submission template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed Patient Access Scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that

has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a Patient Access Scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the Patient Access Scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal'

If you are submitting the Patient Access Scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the appraisal committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the technology and the disease area to which the Patient Access Scheme applies.

NERLYNX® (neratinib) - for the extended adjuvant treatment of adults with early-stage HR+, HER2-overexpressed/amplified breast cancer and who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy

3.2 Please outline the rationale for developing the Patient Access Scheme.

To address any areas of uncertainty that have been raised by the ERG

Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price.

Simple Discount Scheme - Fixed price (which will not vary with any change to the UK list price)

- NHS list price = £4,500 per box of 180 tablets (30 days treatment)

[redacted]

3.3 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

The PAS applies to all patients within the EU licensed population

3.4 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain

criteria, for example, degree of response, response by a certain time point, number of injections? If so:

N/A

3.5 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

N/A

3.6 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

NHS will be invoiced at the PAS price at point of purchase. No rebates will be applicable.

3.7 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

As above and as per completed PASLU template

3.8 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Please refer to PASLU template if required

3.9 Please provide details of the duration of the scheme.

Please refer to PASLU template if required

3.10 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No

3.11 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Company evidence submission template'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

The scheme applies to the same population as in the main company submission.

4.2 If you are submitting the Patient Access Scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the appraisal committee considered to be most plausible. No other changes should be made to the model.

The model submitted to NICE on 17 May 2019 was used to generate results for this template. That version of the model included calculation corrections proposed by the ERG to the original company submission as well as corrections proposed by the company to the ERG amendments. In addition to calculation corrections, the model includes age adjustment to the utilities as proposed by the ERG, implemented with modifications agreed by both the ERG and the company.

4.3 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the appraisal committee considered most plausible.

In the economic model, the PAS has been incorporated directly into the monthly list price of neratinib using the following formula:

- Monthly PAS price of neratinib = Monthly list price × PAS Discount

No other changes have been made to the model.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

Not applicable

4.5 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 3.5 of the 'User guide for company evidence submission template'.

Not applicable

4.6 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the Patient Access Scheme. Please give the reference source of these costs.

Not applicable

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

A suggested format is shown below (table 3).

Table 3 Company base-case cost-effectiveness results without Patient Access Scheme

	Neratinib	Placebo
Intervention cost	£31,860	£6
Subsequent Treatment	£14,163	£27,356
Health State Costs	£1,672	£2,336
Other costs	£2,035	£527
Total costs	£49,731	£30,226
Difference in total costs	+£19,506	
LYG	17.88	17.00
LYG difference	+0.88	
QALYs	13.90	13.16
QALY difference	+0.73	
ICER	£26,687	

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 3 Company base-case cost-effectiveness results with Patient Access Scheme

	Neratinib	Placebo
Intervention cost	[redacted]	£6
Subsequent Treatment	£14,163	£27,356
Health State Costs	£1,672	£2,336
Other costs	£2,035	£527
Total costs	[redacted]	£30,226
Difference in total costs	[redacted]	
LYG	17.88	17.00
LYG difference	+0.88	
QALYs	13.90	13.16
QALY difference	+0.73	
ICER	[redacted]	

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 4 Company base-case incremental results without Patient Access Scheme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Placebo	30,226	17.00	13.16				
Neratinib	49,731	17.88	13.90	+19,506	+0.88	+0.73	26,687

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 5 Company base-case incremental results with Patient Access Scheme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Placebo	30,226	17.00	13.16				
Neratinib	[redacted]	17.88	13.90	[redacted]	+0.88	+0.73	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main company submission of evidence for the technology appraisal. Consider using tornado diagrams.

Figure 1. Tornado diagram for DSA of neratinib vs placebo showing impact on the ICER without PAS (company base case)

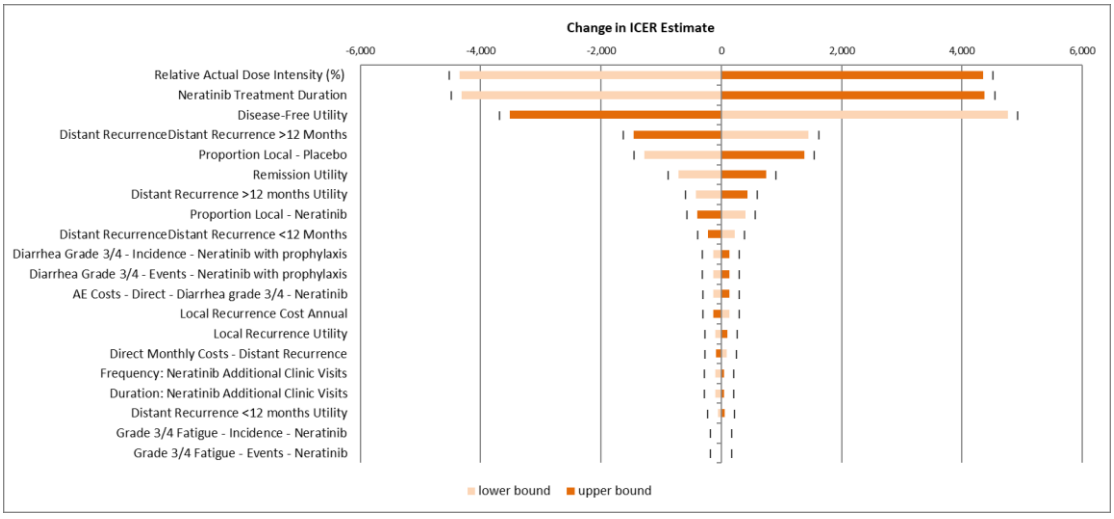

Figure 2. Tornado diagram for DSA of neratinib vs placebo showing impact on the ICER with PAS (company base case)

[redacted]

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Figure 3. Probabilistic sensitivity analysis without PAS: scatter plot (company base case)

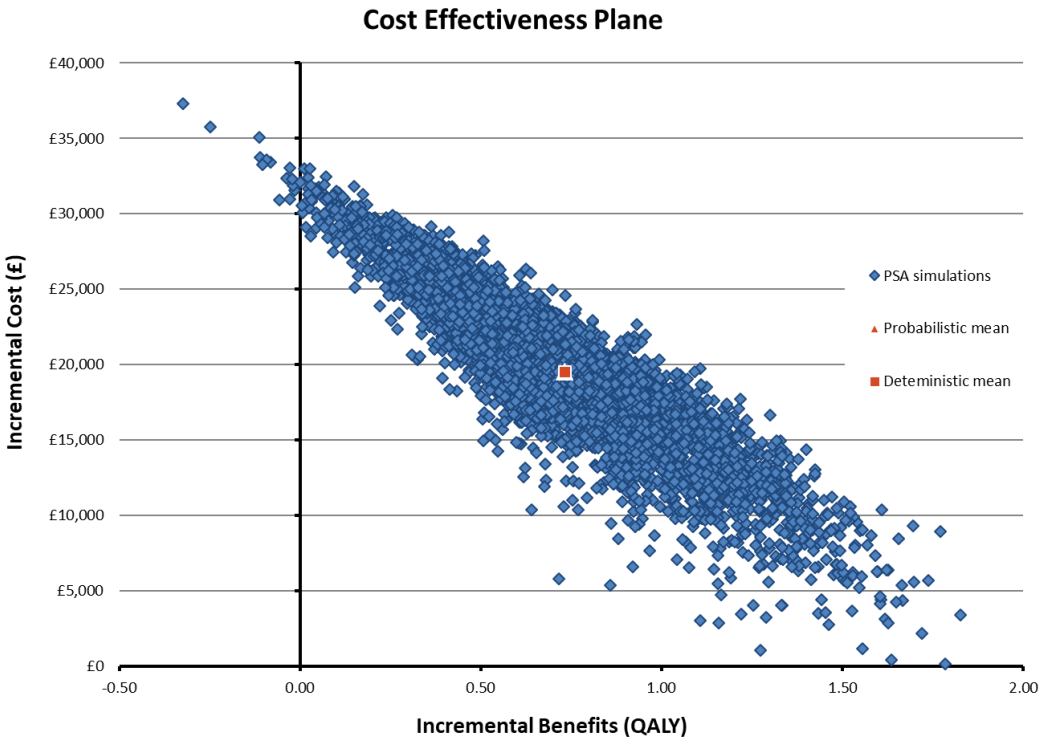

Figure 4. Probabilistic sensitivity analysis with PAS: scatter plot (company base case)

[redacted]

Figure 5. Probabilistic sensitivity analysis without PAS: acceptability curves (company base case)

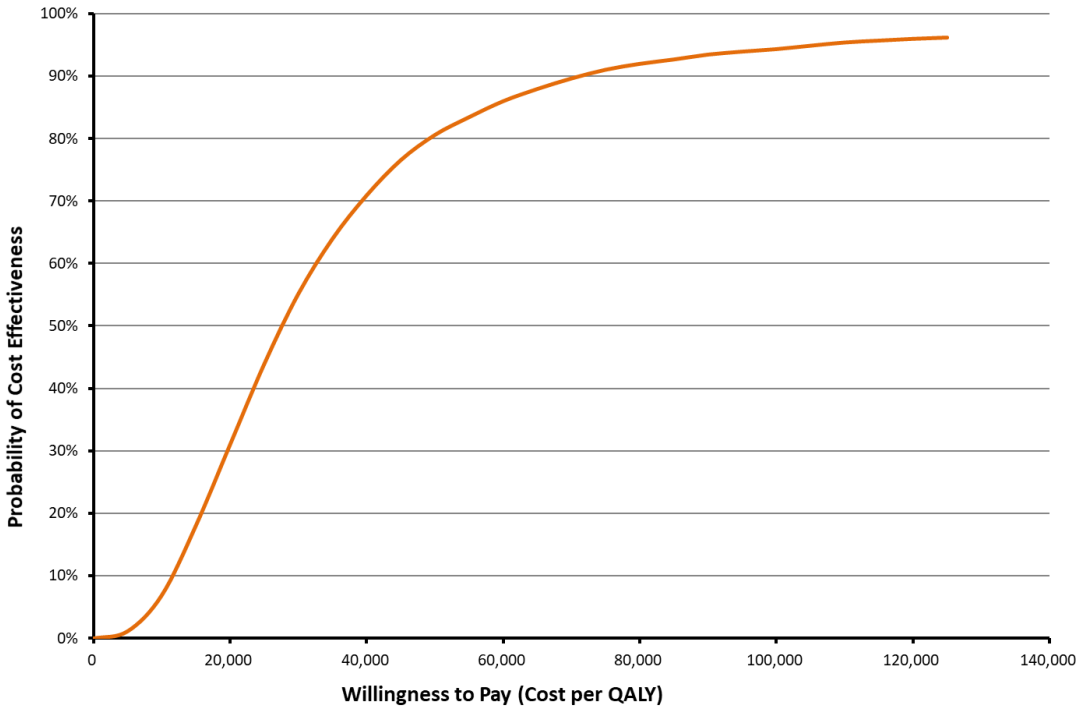

Figure 6. Probabilistic sensitivity analysis with PAS: acceptability curves (company base case)

4.11 Please present scenario analysis results as described for the main company submission of evidence for the technology appraisal.

4.12 If any of the criteria on which the Patient Access Scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the appraisal committee can determine which criteria are the most appropriate to use.

Not applicable

Impact of Patient Access Scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the Patient Access Scheme on the ICERs for the base-case and any scenario analyses. A suggested format is

shown below (see table 5). If you are submitting the Patient Access Scheme at the end of the appraisal process, you must include the scenario with the assumptions that the appraisal committee considered to be most plausible.

As no appraisal committee meeting has been held yet the scenario presented below is based on the ERG alternative base case assumptions for the model. The ERG change to the company base case were:

- iDFS extrapolated with Stratified Generalized Gamma
- Taper of treatment effect 140 months
- Dose intensity 94%
- Alternative utility values for distant recurrence health state

Table 6 Results showing the impact of Patient Access Scheme on ICERs (ERG base case)

	ICER for intervention versus:	
	Placebo	
	Without PAS	**With PAS**
Company base-case	**26,687**	[redacted]
ERG base case	**46,381**	[redacted]

PAS: Patient Access Scheme.

5 Appendix A: Details for outcome-based schemes only

5.1 If you are submitting an outcome based scheme which is expected to result in a price increase, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2 If you are submitting an outcome based scheme which is expected to result in a price reduction or rebate, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.3 Provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection

- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.4 Please specify the period between the time points when the additional evidence will be considered.

Response

5.5 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered.

Response

5.6 Please provide the other data used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.7 Please present the cost-effectiveness results as follows.

- For a scheme that is expected to result in a price increase, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For a scheme that is expected to result in a price reduction or rebate, please summarise in separate tables:

- the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
- the results based on the current evidence and the lower price (if the new evidence is not forthcoming).

A suggested format is shown in table 3, section 4.7.

5.8 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Neratinib for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab [ID981]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm, Monday 17 June 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Dr Ciara O'Brien**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No**

Questions for engagement

Issue 1: The treatment pathway has changed	
a. Would extended adjuvant therapy with neratinib be considered following a neo/adjuvant therapy with pertuzumab, trastuzumab and chemotherapy?	**Yes potentially in a limited patient group with high risk disease; see response Issue 1b**
b. Is it possible for committee to make a recommendation for neratinib for patients who have received a prior pertuzumab therapy? If so, how could the effectiveness be estimated?	**No applicable clinical data on which to base recommendation for neratinib after pertuzumab in the neoadjuvant/ adjuvant setting**
c. If neratinib was recommended as an extended adjuvant therapy would this mean that neratinib would be used instead of adjuvant pertuzumab (as recommended in TA569) for people with hormone receptor positive node-positive disease as clinicians would choose not to use adjuvant therapy with pertuzumab in people with node-positive disease because extended adjuvant therapy with oral neratinib would be available?	**Yes**
d. Would some patients with node positive disease prefer an oral treatment, with neratinib, later in the treatment pathway instead of pertuzumab given intravenously in the adjuvant setting?	**Yes**

Issue 2: Invasive disease-free survival definition in ExteNET	
a. Do you think the trial definition of iDFS that excludes second primary invasive cancer (non-breast cancer) and ductal carcinoma in situ events is suitable for the estimation of overall survival?	**Yes as it captures the majority of events linked to survival outcomes after an early breast cancer diagnosis**
b. Do you think that many events were missed in the neratinib or placebo arm of ExteNET trial because of the iDFS definition used?	**A small number of events – see response to Issue 2a**
Issue 3: Invasive disease-free survival modelling	
a. Which curves look more plausible in relation to the Kaplan-Meier data from the trial? Is the company's or ERG iDFS modelling more appropriate? The effect of the two approaches on cost-effectiveness estimates is large. From looking at the figure in the Appendix of the technical report, would you be able to say which approach is more plausible?	
b. Considering the assumption of general mortality in the model, would you consider that the survival benefit associated with neratinib has been over or underestimated?	
Issue 4: Duration and type of treatment effect	
a. Is it plausible to assume the ERG's tapering of treatment effect of 6.4 years starting after the ExteNET trial for neratinib?	Yes it is plausible
b. Should a shorter taper period, as applied in TA569, be considered instead?	See response Issue 4a

Issue 5: Treatment duration and dose intensity	
a. How should neratinib dose intensity be modelled? Is using the dose based on the ExteNET trial that did not use prophylaxis for diarrhoea appropriate?	Yes
b. How should neratinib treatment duration be modelled? Is using the duration based on the ExteNET trial that did not use prophylaxis for diarrhoea appropriate?	Yes
c. Is the ERG's approach appropriate, or should a different approach be used?	ERG approach is appropriate
Issue 6: Utilities used in the model	
a. Is using the ExteNET utility for iDFS of 0.837 for iDFS and remission appropriate, or is a lower utility value for iDFS more appropriate?	
b. Is using Lidgren et al. 2007 for the remaining states appropriate? This change has a small effect on cost-effectiveness results	
Issue 7: Outstanding issues	
a. Are there any issues which are not covered above which are relevant to the appraisal?	No

NICE National Institute for Health and Care Excellence

Technical engagement response form

Neratinib for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab [ID981]

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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Melanie Sturtevant**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Breast Cancer Care and Breast Cancer Now**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: The treatment pathway has changed	
a. Would extended adjuvant therapy with neratinib be considered following a neo/adjuvant therapy with pertuzumab, trastuzumab and chemotherapy?	
b. Is it possible for committee to make a recommendation for neratinib for patients who have received a prior pertuzumab therapy? If so, how could the effectiveness be estimated?	
c. If neratinib was recommended as an extended adjuvant therapy would this mean that neratinib would be used instead of adjuvant pertuzumab (as recommended in TA569) for people with hormone receptor positive node-positive disease as clinicians would choose not to use adjuvant therapy with pertuzumab in people with node-positive disease because extended adjuvant therapy with oral neratinib would be available?	If neratinib was recommended, we expect that clinicians would make a decision on the best treatment option for this group based on the relative risks and benefits of the treatment in relation to the patient's individual circumstances and preferences. There will also be patients that are not eligible for neo/adjuvant pertuzumab that will be eligible for neratinib ie those with node negative disease that is also hormone receptor positive.
d. Would some patients with node positive disease prefer an oral treatment, with neratinib, later in the treatment pathway instead of pertuzumab given intravenously in the adjuvant setting?	Some patients may prefer an oral treatment later in the pathway. The benefits of potentially spending less time in hospital (if trastuzumab is given subcutaneously – we do not know how many hospitals may now be providing trastuzumab intravenously as a biosimilar) and the convenience of taking an oral treatment would need to be weighed against the extended treatment time with neratinib, and the potential need to take diarrhoea medication.

Issue 2: Invasive disease-free survival definition in ExteNET	
a. Do you think the trial definition of iDFS that excludes second primary invasive cancer (non-breast cancer) and ductal carcinoma in situ events is suitable for the estimation of overall survival?	The definition of IDFS in the APHINITY trial for adjuvant pertuzuamb also excluded second primary non-breast cancer events and DCIS. In that appraisal the Committee acknowledged that, in the absence of overall survival data, IDFS was the only data available for decision making. It would seem iniquitous for the Committee to reach a different conclusion on this issue for this appraisal.
b. Do you think that many events were missed in the neratinib or placebo arm of ExteNET trial because of the iDFS definition used?	
Issue 3: Invasive disease-free survival modelling	
a. Which curves look more plausible in relation to the Kaplan-Meier data from the trial? Is the company's or ERG iDFS modelling more appropriate? The effect of the two approaches on cost-effectiveness estimates is large. From looking at the figure in the Appendix of the technical report, would you be able to say which approach is more plausible?	
b. Considering the assumption of general mortality in the model, would you consider that the survival benefit associated with neratinib has been over or underestimated?	
Issue 4: Duration and type of treatment effect	
a. Is it plausible to assume the ERG's tapering of treatment effect of 6.4 years starting after the ExteNET trial for neratinib?	

b. Should a shorter taper period, as applied in TA569, be considered instead?	
Issue 5: Treatment duration and dose intensity	
a. How should neratinib dose intensity be modelled? Is using the dose based on the ExteNET trial that did not use prophylaxis for diarrhoea appropriate?	
b. How should neratinib treatment duration be modelled? Is using the duration based on the ExteNET trial that did not use prophylaxis for diarrhoea appropriate?	
c. Is the ERG's approach appropriate, or should a different approach be used?	
Issue 6: Utilities used in the model	
a. Is using the ExteNET utility for iDFS of 0.837 for iDFS and remission appropriate, or is a lower utility value for iDFS more appropriate?	
b. Is using Lidgren et al. 2007 for the remaining states appropriate? This change has a small effect on cost-effectiveness results	
Issue 7: Outstanding issues	
a. Are there any issues which are not covered above which are relevant to the appraisal?	

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Neratinib (NERLYNX®) for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab

ADDENDUM

Revised cost-effectiveness analyses based on PAS prices for neratinib

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 25/06/2019

1. Update of the company cost-effectiveness results with neratinib PAS price

The company applied for a patient access scheme (PAS) simple discount on the list price of neratinib at the point of acquisition by the National Health Service (NHS). The proposed discount is [redacted].

The results presented in this section are updated results of the company base-case, sensitivity and scenario analyses with the PAS for neratinib included. The economic model used to conduct all the analyses in this addendum document was the model submitted to National Institute for Health and Clinical Excellence (NICE) on 17 May 2019, which included corrections proposed by the Evidence Review Group (ERG) to the original model, corrections proposed by the company to the ERG amendments and age adjustment to the utilities as proposed by the ERG, implemented with modifications agreed by both the ERG and the company after the technical engagement (TE) meeting. Only discounted results are presented.

1.1 Company base-case results

Table 1 shows the company base-case results with the PAS price for neratinib. The estimated incremental cost-effectiveness ratio (ICER) was [redacted], which is [redacted] lower than the company base-case ICER (post TE corrections) obtained with neratinib list-price (£26,687).

Table 1: Deterministic base-case results (neratinib PAS price)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Neratinib	[redacted]	17.88	13.90	[redacted]	0.88	0.73	[redacted]
Placebo	£30,226	17.00	13.16				

Based on Table 6 in the addendum to the CS.[1]
CS = company submission; ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALYs = quality-adjusted life years

1.2 Company probabilistic sensitivity analysis results

Table 2 shows the probabilistic sensitivity analysis (PSA) results based on the company's base-case with the PAS price for neratinib. The estimated ICER was [redacted], which is in line with the deterministic ICER shown in Table 1.

Table 2: Probabilistic base-case results (neratinib PAS price)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Neratinib	[redacted]	NR	13.86	[redacted]	NR	0.73	[redacted]
Placebo	[redacted]	NR	13.13				

Source: ERG based on PSA data from the company's model.
ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; PSA = probabilistic sensitivity analysis: QALYs = quality-adjusted life years

The plot of the PSA outcomes in the cost effectiveness (CE) plane shown in Figure 1 indicates that almost [redacted]% of the simulated cohorts resulted in a gain in quality-adjusted life years (QALYs). From these, [redacted]% are in the north-east quadrant of the CE-plane, where neratinib provides more QALYS than placebo but at higher costs, and [redacted]% are in the south-east quadrant of the CE-plane, where neratinib dominates placebo. Finally, [redacted]% are in the north-west quadrant of the CE-plane, where

placebo dominates neratinib. The cost effectiveness acceptability curve (CEAC) in Figure 2 shows that at £20,000 and £30,000 willingness to pay, the probability of neratinib being cost effective is [redacted]% and [redacted]%, respectively.

Figure 1: Scatterplot from the probabilistic sensitivity analysis iterations (neratinib PAS price)

Based on Figure 4 in the addendum to the company submission.[1]
PAS = patient access scheme; QALY = quality-adjusted life year

Figure 2: Cost effectiveness acceptability curve (neratinib PAS price)

Based on Figure 6 in the addendum to the company submission.[1]
PAS = patient access scheme; QALY = quality-adjusted life year

1.3 Company deterministic sensitivity analysis results

Figure 3 presents the tornado diagram that shows the most influential parameters on the ICER from the deterministic one-way sensitivity analysis. It can be seen that the ICER was most sensitive to changes in neratinib treatment duration and dose intensity. In any case, these ICERs differed less than [redacted], in absolute value, with the company base-case ICER.

Figure 3: Tornado diagram (neratinib PAS price)

Source: Figure 2 in the addendum to the company submission.[1]
ICER = incremental cost-effectiveness ratio; PAS = patient access scheme

ERG comment: As mentioned in the ERG report,[2] the tornado diagram presented by the company was obtained allowing 10% variation from mean value for all parameters. This was deemed arbitrary by the ERG and may not represent an equally plausible range of variation for all input parameters. This was not changed by the company in the most recent version of the electronic model. Therefore, the tornado diagram presented above should be interpreted with caution. For that reason, deterministic sensitivity analysis results will not be presented by the ERG in the remaining of this addendum document.

2. Update of the ERG cost-effectiveness results with neratinib PAS price

The results presented in this section are updated results of the ERG base-case, PSA and several scenario analyses with the PAS price for neratinib included. Note that, unlike in the original company submission, the age-adjusted utility decline from Janssen and Szende 2014[3] was assumed by the company in their current base-case. Therefore, the assumptions changed by the ERG for its preferred base-case (presented in Section 7.1.2 of the ERG report[2]) are listed below:

1. Treatment effectiveness: Modelling invasive disease-free survival (iDFS) according to a stratified generalised Gamma distribution.
2. Treatment effectiveness: Declining neratinib treatment effect up to month 140. This is the time point where the hazard rates of the iDFS stratified generalised Gamma distribution and the flexible Weibull (2 knots) distribution for the general population mortality are equal.
3. Utilities: Trial data for iDFS health state and Lidgren et al. 2007 utilities for the other health states.[4]
4. Resource use and costs: Neratinib dose intensity equal to [redacted]%.

Following the technical engagement meeting, the company acknowledged the uncertainty surrounding the impact of antidiarrhoeal prophylaxis on the dose received and costs. However they argued that if the dose intensity or duration were increased, the efficacy would also improve. Since we do not have this efficacy data, they argued that it was unfair to adjust the costs. The ERG argue that the impact on efficacy is also uncertain, as it may or may not increase and this could also impact AE profiles. However to avoid additional uncertainty, the ERG removed the increased dose intensity from the base-case and reserved this for scenario analysis.

Only discounted results are presented in the remaining of this addendum document.

2.1 ERG base-case results

Table 3 shows the ERG base-case results. The ICER in the ERG preferred base-case, after implementing the changes listed above (including removing the assumption of increased dose intensity) and the neratinib PAS price, was [redacted], which is [redacted] lower than the ERG base-case ICER obtained with neratinib list-price (£46,381).

Table 3: Deterministic ERG base-case results (neratinib PAS price)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Neratinib	[redacted]	17.84	13.91	[redacted]	0.69	0.54	[redacted]
Placebo	£27,677	17.15	13.37				

Source: ERG based on results from the company's model.
ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALYs = quality-adjusted life years

2.2 ERG probabilistic sensitivity analysis results

Table 4 shows the PSA results based on the ERG's base-case assuming the PAS price for neratinib. The estimated ICER was [redacted], which is in line with the deterministic ICER shown in Table 3.

Table 4: ERG PSA results (neratinib PAS price)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER
Neratinib	[redacted]	NR	13.76	[redacted]	NR	0.52	[redacted]
Placebo	£29,187	NR	13.24				

Source: ERG based on PSA data from the company's model.
ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years

The plot of the PSA outcomes in the CE-plane shown in Figure 4 indicates that almost [redacted]% of the simulated cohorts resulted in a gain in QALYs. From these, [redacted]% are in the north-east quadrant of the CE-plane, where neratinib provides more QALYs than placebo but at higher costs, and [redacted]% are in the south-east quadrant of the CE-plane, where neratinib dominates placebo. Finally, [redacted]% are in the north-west quadrant of the CE-plane, where placebo dominates neratinib. The CEAC in Figure 5 shows that at £20,000 and £30,000 willingness to pay, the probability of neratinib being cost effective is [redacted]% and [redacted]%, respectively.

Figure 4: Scatterplot from the probabilistic sensitivity analysis iterations (neratinib PAS price)

Source: ERG based on PSA data from the company's model
PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5: Cost effectiveness acceptability curve (neratinib PAS price)

Source: ERG based on PSA data from the company's model
PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

2.3 Scenario and subgroup analysis results

The results of the additional scenarios conducted by the ERG were shown in Section 7.2.2 of the ERG report.[2] Since the ERG base-case with the neratinib PAS price and most of the results of the scenario analyses presented in the ERG report had a relatively minor impact on the ICER, a pragmatic approach was taken by the ERG in this addendum document. Thus, instead of presenting results from all the scenarios in the ERG report with the neratinib PAS price, only those for which a larger impact on the ICER was observed, and consequently might result in ICERs , are presented below.

Additional scenario 1: changing iDFS parametric distributions

The ERG assessed the impact of using different parametric survival curves for extrapolating of iDFS beyond the duration of the ExteNET trial. In Table 5, the results are displayed indicating the corresponding taper period for each distribution. Note the total duration of the treatment effect is calculated as the follow-up time in ExteNET (62.98 months) plus the taper period (e.g. in the ERG base-case this was 77.02 months, so the total duration of the treatment effect was 140 months). The scenario with the largest ICER ( ) was obtained assuming a generalised Gamma distribution, which was criticised by the company, as mentioned in section 5.2.6.1 of the ERG report.[2] This was the only scenario with an ICER .

Table 5: ERG iDFS scenario analyses (neratinib PAS price)

Distribution [taper period in months]	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Stratified generalised gamma [77.02]*	[redacted]	13.91	£27,677	13.37	[redacted]	0.54	[redacted]
Stratified flexible Weibull (1 knot) [234.02]	[redacted]	13.93	£30,255	13.25	[redacted]	0.68	[redacted]
Flexible Weibull (1 knot) [113.02]	[redacted]	13.92	£27,677	13.37	[redacted]	0.56	[redacted]
Flexible Weibull (2 knots) [111.02]	[redacted]	13.87	£30,033	13.26	[redacted]	0.61	[redacted]
Generalised Gamma [76.02]	[redacted]	13.79	£26,329	13.44	[redacted]	0.35	[redacted]

Source: Based on electronic model
*ERG preferred base-case
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year

Additional scenario 2: changing the duration of the treatment effect

In all these scenarios, the iDFS distribution was the stratified generalised Gamma as in the ERG base-case. The maximum taper period for this distribution was 140 months. In the ERG report, the impact of assuming different (shorter) taper periods was assessed. In this addendum document, the ERG also took a pragmatic approach and assessed the impact of the most and the least favourable scenario for neratinib only, namely:

- a taper period of 0 months (i.e. no continuation of the treatment effect after the trial period),
- the treatment effect observed at the end of the five-year follow-up was maintained until the patients had equal risk of an iDFS event as the general population. This implicitly means that there is a waning of the treatment effect starting at month 130 with a taper of effect over the next 3.83 years (month 176) at which point no further treatment effect is included in the model.

The results of these scenarios are shown in Table 6. It can be seen that even for the least favourable scenario for neratinib, the ICER was [redacted]. Note that assuming taper periods shorter than 77.02 months (the one assumed in the ERG base-case), would result in ICERs ranging between [redacted] and [redacted].

Table 6: ERG duration of the treatment effect scenario analyses (neratinib PAS price)

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Taper period of 0 months	[redacted]	13.83	£27,677	13.37	[redacted]	0.47	[redacted]

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Taper period of 77.02 months*	[redacted]	13.91	£27,677	13.37	[redacted]	0.54	[redacted]
Continued treatment effect	[redacted]	13.94	£27,677	13.37	[redacted]	0.58	[redacted]

Based on electronic model
* ERG preferred base-case
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year

Additional scenario 3: neratinib treatment duration and dose intensity

The ERG assessed the impact of assuming different treatment durations and dose intensities for neratinib on the cost effectiveness results. In Table 7, results are shown for the scenarios assuming a dose intensity of [redacted]%, a dose intensity as in the original ERG base case ([redacted]%) (half way between [redacted]% and 100%), a treatment duration of 12 months, a treatment duration of [redacted] months (halfway between [redacted] and 12 months), and the combination of a dose intensity of [redacted]% with a treatment duration of 12 months (as 'prescribed per protocol'). In the scenarios assuming an increased dose intensity, all ICERs remained [redacted]. The duration of the treatment effect had a larger impact on the ICER and, in the two scenarios explored, the ICER was [redacted]. When the neratinib dose intensity and duration were considered as prescribed, the ICER was [redacted].

Table 7: ERG treatment duration and dose intensity scenario analyses (neratinib PAS price)

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
ERG preferred base-case (now [redacted]%)	[redacted]	13.91	£27,677	13.37	[redacted]	0.54	[redacted]
Dose intensity [redacted]%	[redacted]	13.91	£27,677	13.37	[redacted]	0.54	[redacted]
Dose intensity [redacted] (half way between base-case and 100%	[redacted]	13.91	£27,677	13.37	[redacted]	0.54	[redacted]
Treatment duration of 12 months	[redacted]	13.91	£27,677	13.37	[redacted]	0.54	[redacted]

Scenario	Neratinib		Placebo		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Treatment duration of [redacted] months	[redacted]	13.91	£27,677	13.37	[redacted]	0.54	[redacted]
Dose intensity [redacted]% + treatment duration of 12 months	[redacted]	13.91	£27,677	13.37	[redacted]	0.54	[redacted]

Based on electronic model

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year

3. Comparison of company and ERG base-case ICERs with and without neratinib PAS price

Table 8 summarises the company and ERG base-case results presented in the ERG report (assuming neratinib list price) and in this addendum document (assuming neratinib PAS price). These results also show the induvial and cumulative impact of the ERG preferred assumptions on the ICER.

Table 8: Deterministic company and ERG base-case results with neratinib list price and with neratinib PAS price

Alteration	Notes	List price ICER (£/QALY)	PAS price ICER (£/QALY)
Company base-case pre TE	Model corrected for small error	£24,180	[redacted]
Company base-case post TE	Utility decrement with age assumed	£26,687	[redacted]
Lidgren et al. 2007{#100} utility for distant recurrence state instead of Lloyd et al. 2006{#183}	TE Issue 6 – Utilities used in the model	£28,289	[redacted]
Using stratified generalised gamma to model iDFS instead of flexible-spline Weibull with 1 knot	TE Issue 3 – Invasive disease-free survival modelling	£36,492	[redacted]
Declining treatment effect at 140 months (11.67 years) instead of 166.8 moths (13.9 years).	TE Issue 4 – Duration and type of treatment effect	£36,026	[redacted]
Neratinib dose intensity equal to [redacted]%.	TE Issue 5 – Treatment duration and dose intensity	£29,753	[redacted]
Cumulative impact of 1-2 assumptions on the cost-effectiveness estimate	-	£38,560	[redacted]
Cumulative impact of 1-3 assumptions on the cost-effectiveness estimate (ERG's base case)	-	£42,242	[redacted]
Cumulative impact of 1-4 assumptions on the cost-effectiveness estimate (ERG's base case)	Model corrected for small error	£46,381	[redacted]

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; iDFS = invasive disease-free survival; PAS = Patient Access Scheme; QALY = quality adjusted life year; TE = Technical Engagement

4. REFERENCES

[1] National Institute for Health and Care Excellence. *Patient Access Scheme submission. Neratinib (NERLYNX®) for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab [ID981]. Submitted by Pierre Fabre Ltd*. London: National Institute for Health and Care Excellence, 2019. 17p.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Neratinib for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab [ID981]

1. Summary of the draft technical report

1.1 This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: July 2019

1.2 In summary, the technical team considered the following:

Issue 1 **– for discussion.** Since this appraisal was scoped, the treatment pathway has changed. TA569 (March 2019) where pertuzumab, with trastuzumab and chemotherapy, was recommended for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults, if they have lymph node-positive disease. **There are no data available to demonstrate the efficacy of neratinib in the extended adjuvant setting of early breast cancer following a treatment regimen that includes pertuzumab. Adjuvant pertuzumab is only recommended for lymph node-positive disease in (TA569). Over 80% people in the ExteNET trial had lymph node-positive disease.**

Issue 2 **– agreed.** The invasive disease free survival (iDFS) definition used in the ExteNET trial is less inclusive than normal. **In the absence of overall survival (OS) data, iDFS is suitable for decision making. However, as a surrogate outcome is used to model OS, the estimated OS is uncertain.**

Issue 3 **– for discussion.** There is uncertainty about how long people remain disease free. The technical team agrees with the ERG that extrapolation based on the stratified generalised gamma distribution for iDFS modelling is more plausible than the company's approach as it provided the best overall fit to the data as the proportional hazards assumption is not met. **The company's use of general population mortality in the model is appropriate. However, as noted earlier, OS estimates based on iDFS are uncertain.**

Issue 4 **– for discussion.** The treatment effect duration after ExteNET trial follow-up is uncertain. The ERG's approach assuming a tapering of treatment effect with neratinib of 6.42 years, starting after the ExteNET trial follow-up at 5 years and finishing when the extrapolated iDFS curves cross the general mortality at 140 months (11.67 years) **is appropriate for**

decision making although the company consider this a conservative assumption.

Issue 5 **– agreed. Neratinib dose and duration based on ExteNET are appropriate for decision making**. However, as no diarrhoea prophylaxis was used in ExteNET, there is uncertainty around the impact of anti-diarrhoeal prophylaxis on neratinib clinical and cost-effectiveness.

Issue 6 **– agreed. Age-adjusted utilities, ExteNET value for disease-free state, and Lindgren et al. 2007 value for distant recurrence are suitable for decision making.** However, the utility value for the disease-free state is uncertain. A protocol amendment (October 2011) removed the requirement for EQ-5D-3L data collection in ExteNET. The disease-free state utility of 0.837 was estimated with large numbers of missing data.

1.3 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The clinical trial evidence in ExteNET trial is immature. The final OS analysis is expected in [redacted] for the full trial population and in [redacted] for the label population.
- ExteNET trial (n=2,840) was not designed to have statistical power to detect differences between treatment-effects in the 'label population' (n=1,334), a subgroup of ExteNET trial, that reflects the marketing authorisation population and that is the basis for the company submission.
- Only 80 patients at 13 sites in the UK were recruited in ExteNET, and only 41 (19 in the neratinib arm and 22 in the placebo arm) of these were in the label population (n=1,334).
- The incidence and mean number of events of diarrhoea with prophylaxis using loperamide was obtained from the safety population

of the CONTROL trial. The CONTROL trial is an ongoing, phase 2 open-label, safety and tolerability study investigating the effect of anti-diarrhoeal strategies on the incidence of neratinib-associated diarrhoea in early-stage HER2-positive breast cancer patients, who have previously undergone a course of trastuzumab therapy in the adjuvant setting. This population does not match ExteNET label population in terms of length of time from trastuzumab or hormone receptor status.

- In the company base-case, the cost of subsequent treatments following recurrence was assumed to be £175,390. This value was taken from the TA569 appraisal. Treatments and the market share of treatments identified through expert elicitation differed somewhat from those obtained from TA569.

- Deterministic sensitivity analyses were calculated using +/- 10 % of the model values, instead of using 95% Confidence Intervals.

1.4 The cost-effectiveness results include a commercial arrangement (patient access scheme) for neratinib.

1.5 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY gained (see Table 1: Impact of key issues assumptions on the cost-effectiveness estimate). However, many of the assumptions used in the model are uncertain (Issue 3 – Invasive disease-free survival modelling - Issue 6 –Utilities used in the model), therefore the most plausible ICER is unknown and could be higher or lower than [redacted] per QALY gain. In addition, assumptions and inputs summarised in Table 2: Outstanding uncertainties in the evidence base, and Table 3: Other issues for information, introduce further uncertainty to the cost-effectiveness estimate.

1.6 No equality issues were identified.

Issue 1 – The treatment pathway has changed – for discussion

Background/description of issue	Neratinib has a marketing authorisation for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive, HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy. ExteNET (n=2,840) is a phase 3 randomised controlled trial that compared neratinib treatment with placebo in women aged 18 years or older (≥20 years in Japan) with HER2-positive breast cancer who had completed adjuvant trastuzumab therapy within 2 years. The company based its submission on a subgroup of ExteNET trial that matches neratinib marketing authorisation, the label population (n=1,334). Pertuzumab, with trastuzumab and chemotherapy, was recommended in March 2019 for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults, if they have lymph node-positive disease (TA569). Pertuzumab, in combination with trastuzumab and chemotherapy, is recommended, within its marketing authorisation, as an option for the neoadjuvant treatment of adults with HER2-positive breast cancer at high risk of recurrence (TA424; December 2016). In ExteNET, prior therapy with HER1 and/or HER2 therapy other than trastuzumab was not permitted. **The company** in response to **ERG's clarification questions** (questions A6 and A8) noted that although pertuzumab and neratinib both target HER2, their modes of action are different. Pertuzumab is an intravenous biological therapy that targets the extracellular domains of HER2 via antibody-dependent, cell-mediated cytotoxicity. Neratinib is an oral, small molecule tyrosine kinase inhibitor that binds irreversibly to the intracellular domains of EGFR, HER2, and HER4, or their active heterodimers with HER3, simultaneously blocking their downstream signalling pathways. They considered that the addition of neratinib following on from any adjuvant therapy with trastuzumab and pertuzumab or following from neoadjuvant therapy with pertuzumab is expected to provide additional efficacy in the extended adjuvant setting on top of the benefit provided by previous trastuzumab-based therapy, as currently there is no further HER2-directed therapy beyond one year of trastuzumab. They also noted that, in CONTROL, neoadjuvant pertuzumab was permitted and that 40.1% of patients in the loperamide cohort had received neoadjuvant pertuzumab. The CONTROL trial is an ongoing (estimated enrolment=750), phase 2 open-label, safety and tolerability study investigating the effect of anti-diarrhoeal strategies (loperamide, loperamide plus budesonide, and loperamide plus colestipol prophylaxis) on the incidence of neratinib-associated diarrhoea in early-stage

HER2-positive breast cancer patients, who have previously undergone a course of trastuzumab therapy in the adjuvant setting.

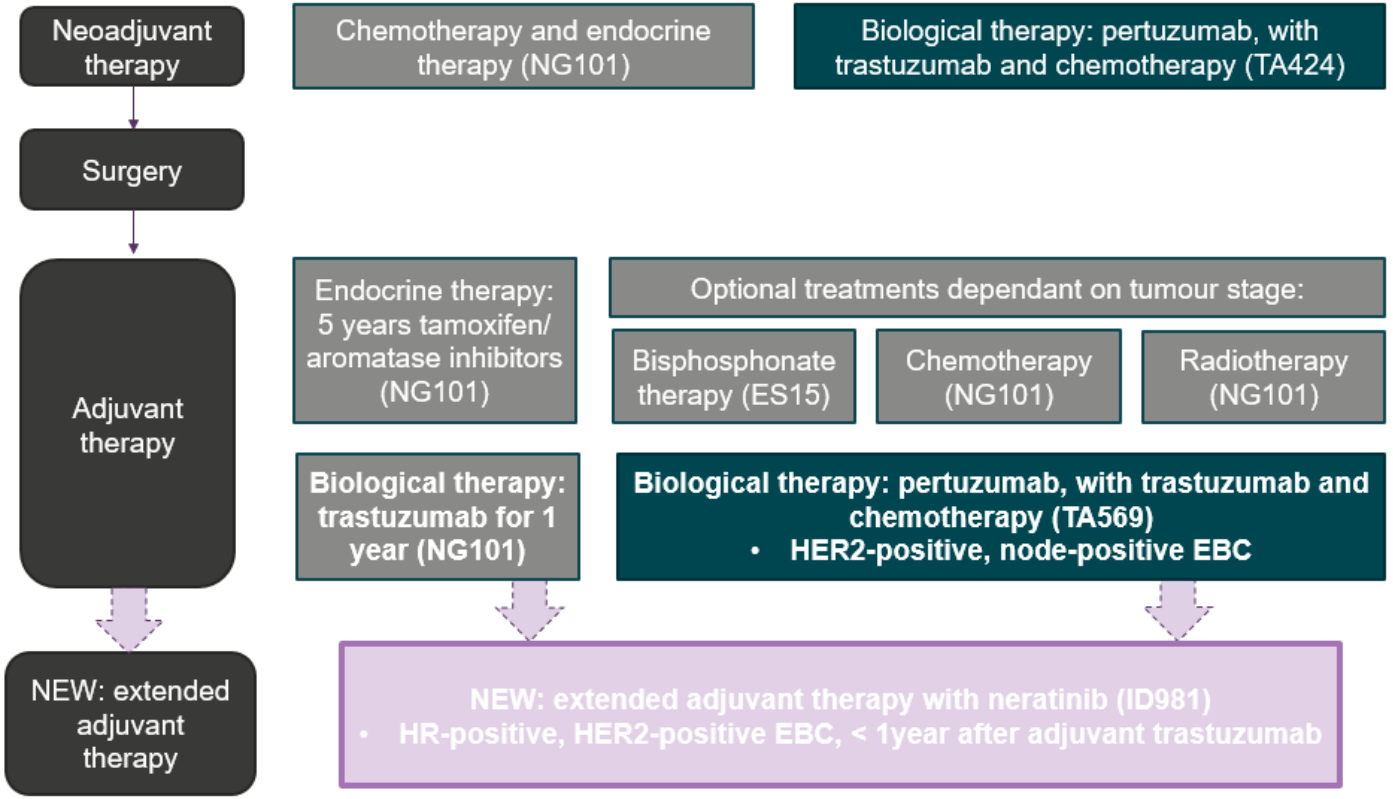

Figure 1 Neo/adjuvant, early and locally advanced breast cancer, pathway

	The technical team notes that TA569 recommendations are based on a subgroup of people with lymph node-positive disease (n=3,005) in APHINITY trial (n=4,804). APHINITY is a phase 3 randomised controlled trial that compared the addition of pertuzumab to chemotherapy and trastuzumab with placebo in adults with operable HER2-positive primary breast cancer. While the current appraisal is based on the ExteNET hormone receptor positive subgroup of patients who have completed a course of adjuvant trastuzumab <1 year ago (label population). Although a protocol amendment limited recruitment to node-positive disease, 19.4 % of people in neratinib and 18.8 % of people in placebo arm of the ExteNET label population had node-negative disease. **Error! Reference source not found.** reflects the anticipated clinical practice if n eratinib was recommended as an option for extended adjuvant therapy.
Why this issue is important	It is important to know where in clinical practice neratinib will be used.
Technical team judgement before engagement	The technical team do not know whether the effectiveness of neratinib based on the ExteNET trial (following adjuvant treatment with trastuzumab) can be assumed to be beneficial in patients who have received pertuzumab with trastuzumab and chemotherapy.
Summary of comments	**Comments received from sponsor company Pierre Fabre:** • There are no data available to demonstrate the efficacy of neratinib in the extended adjuvant setting of early breast cancer following a treatment regimen that includes pertuzumab. • The different mechanism of action of neratinib means that the addition of neratinib following any adjuvant therapy with pertuzumab is likely to provide additional efficacy in the extended adjuvant setting. • Clinicians would make a decision on the best treatment option based on an assessment of the risk/benefit profile of the two medicines along with the patient's individual clinical situation. • Some patients may prefer an oral treatment, but other factors would also be taken into account by clinicians when deciding on the most appropriate treatment regimen. • A naive comparison of iDFS rates indicates a higher rate for neratinib compared with pertuzumab. • Clinicians may choose not to use adjuvant therapy with pertuzumab in patients eligible for neratinib if neratinib becomes available in the extended adjuvant setting.

	Comments received from Breast Cancer Care and Breast Cancer Now: • Clinicians would make a decision on the best treatment option based on the relative risks and benefits of the treatment in relation to the patient's individual circumstances and preferences • The benefits of potentially spending less time in hospital (if trastuzumab is given subcutaneously) and the convenience of taking an oral treatment would need to be weighed against the extended treatment time with neratinib, and the potential need to take diarrhoea medication. • People with node negative disease that is also hormone receptor positive are not eligible for neo/adjuvant pertuzumab but would be eligible for neratinib. **Comments received from a clinician expert:** • Following prior pertuzumab therapy, neratinib could be potentially considered in a limited patient group with high risk disease. However, there are no applicable clinical data on which to base recommendation for neratinib after pertuzumab. • If neratinib was recommended, clinicians could choose not to use adjuvant therapy with pertuzumab in people with node-positive disease. • Some patients with node positive disease may prefer an oral treatment, with neratinib, later in the treatment pathway instead of pertuzumab given intravenously in the adjuvant setting.
Technical team scientific judgement after engagement	There are no data available to demonstrate the efficacy of neratinib in the extended adjuvant setting of early breast cancer following a treatment regimen that includes pertuzumab. Adjuvant pertuzumab is only recommended for lymph node-positive disease. For patients with lymph node-positive disease the decision on the best treatment option would be based on the patient's individual circumstances and preferences, however there is no evidence directly or indirectly comparing extended adjuvant therapy with neratinib with pertuzumab-based adjuvant therapy.

Issue 2 –Invasive disease-free survival definition in ExteNET - agreed

Background/description of issue	Disease-free survival (DFS) is often used as a surrogate end point for overall survival. However, definitions of DFS often differ amongst individual trials. Recent studies have used invasive DFS (iDFS) as a compound surrogate outcome for overall survival that incorporates both distant and loco-regional recurrence. **The company** (CS section B.2.3.1.1 page 28) stated that iDFS is the primary endpoint in ExteNET trial and defined it as time from randomisation to the first occurrence of the following events: • Invasive ipsilateral breast tumour recurrence • Invasive contralateral breast cancer • Local/regional invasive recurrence • Distant recurrence • Death from any cause **The ERG** explained that, the ExteNET definition is narrower than the DATECAN (Definition for the Assessment of Time-to-event Endpoints in CANcer trials) guidelines iDFS definition and that second primary invasive cancer (non-breast cancer) and ductal carcinoma in situ were not included in the definition, however they noted that the definition was published after the trial had started. **The technical team** noted that a similar iDFS definition was used in a recent appraisal of pertuzumab for adjuvant treatment of HER2-positive early breast cancer (TA569; APHINITY trial). Although DFS measures reported in APHINITY were all relatively similar, there was a significant difference between iDFS measures and overall survival (OS). Unfortunately, ExteNET OS data are not currently available for a comparison with iDFS (for more see Issue 3 – Invasive disease-free survival modelling). **The technical team** is concerned that some iDFS events might have been missed in both arms of the ExteNET trial and whether this outcome is a suitable surrogate outcome to estimate OS in the model.
Why this issue is important	It is important to ascertain whether the ExteNET iDFS definition is a useful surrogate for the estimation of OS.

Technical report template 2 – AFTER technical engagement

Technical team judgement before engagement	The iDFS definition as used in ExteNET is relevant to this appraisal, although we are unsure how useful the definition is and, how good it is as a surrogate for OS.
Summary of comments	**Comments received from sponsor company Pierre Fabre:** • The definition of iDFS was standard when ExteNET protocol was developed and based on STEEP criteria (Hudis et al., 2007). • An addendum to the DATECAN publication excluded ductal carcinoma in situ from the definition, which is therefore not included in the current DATECAN definition of iDFS (Gourgou-Bourgade et al., 2015). • Rates of second primary invasive cancer are low, therefore, this definition of iDFS is still expected to correlate with OS. **Comments received from Breast Cancer Care and Breast Cancer Now:** • In TA569, the committee concluded that in the absence of overall survival data, iDFS was the only data available for decision making. **Comments received from a clinician expert:** • iDFS definition is suitable for the estimation of OS as it captures the majority of events linked to survival outcomes after an early breast cancer diagnosis.
Technical team judgement after engagement	In the absence of OS data, iDFS is suitable for decision making. However, as a surrogate outcome is used to model OS, the estimated OS is uncertain.

Issue 3 – Invasive disease-free survival modelling – for discussion

Background/description of issue	**The company** (CS section B3.2.2 page 88) developed a five-state Markov model to evaluate the cost-effectiveness of neratinib (iDFS, local recurrence, remission, distant recurrence and dead). In the absence of overall survival (OS) data, iDFS in the label population of the ExteNET trial and a general population mortality rate was used to estimate OS (CS section B.3.3.1 page 91 and Appendix). The company did not find evidence against the proportional hazards assumption and iDFS data in the label population were pooled and modelled together with a treatment effect as a covariate. The company chose a flexible-spline Weibull with 1 knot to model iDFS and the same distribution, but with 2 knots, to model general population mortality (Figure 3 in Appendix**Error! Reference source not found.**). **The ERG** (ERG report 5.2.6.1 page 61) explained that, there is at least uncertainty regarding the assumption of proportional hazards as some the analyses provided by the company suggested that the assumption is not valid. For example, analyses of the hazard rates and hazard ratio suggested that proportional hazards do not hold for iDFS and that the hazard ratio is not constant over time (CS figures 32 and 33; page 99 and 100), so the ERG explored stratified models for which the proportional hazard assumption is not needed. In addition, the ERG considered that the company's selection of parametric models was not comprehensive and consistent. The ERG therefore assessed an overall-goodness-of-fit to the models considered by the company and stratified models provided by the ERG (Table 5.3 in the ERG report; page 76). They found that the stratified generalised gamma provided the best overall fit for the iDFS data and included this model in its preferred base-case (Figure 3 in Appendix). Similarly to the company, the ERG used a flexible-spline Weibull with 2 knots to model general population mortality. They further explained, that the company assumed that, death due to breast cancer is only possible from the distant recurrence health state and that this assumption is likely to underestimate the cost-effectiveness. For all the other health states, mortality risk was modelled according to age-adjusted survival probabilities for the female general population. However, it is questionable that the mortality of those in the states of iDFS, local recurrence and remission is that of the general population, particularly given the absence of OS data. **The technical team** notes that although both approaches may be plausible, stratified models for which the proportional hazard assumption is not needed may be more appropriate. The ERG's approach provides the best overall fit for the iDFS, however the use of general population mortality in the model is underestimating the resulting ICER.

Why this issue is important	This single change to the modelling has a large impact on the cost-effectiveness results with the resulting ICERs being significantly higher that the company's base-case.
Technical team judgement before engagement	The technical team agrees with the ERG and incorporated the ERG's stratified approach to iDFS modelling in Table 1: Impact of key issues assumptions on the cost-effectiveness estimate. However, it is concerned that the OS estimates based on iDFS modelling are uncertain.

Summary of comments	**Comments received from sponsor company Pierre Fabre:**
	• Both distributions provide a very good fit to the Kaplan-Meier data within the trial period, it is difficult to distinguish between the two within the trial period.
	• There is no clear evidence that the proportional hazard assumption does not hold, and statistical testing shows that survival analysis is more likely to be proportional hazards than not.
	• Pierre Fabre is willing to accept the consideration of non-proportional hazards and the stratified generalised gamma curve as a conservative approach. However, we would highlight that there is a high degree of uncertainty around this assumption and consider this approach to be representing the high end of the most plausible ICERs.
	• Pierre Fabre considers that the assumption around general population mortality in the local recurrence health state in the model is appropriate, and neither over- nor under-estimates survival. Clinical evidence suggests that very few patients die from breast cancer having experienced a local recurrence only, they are most likely to move into the distant recurrence health state first:
	  ○ No patients in ExteNET recorded as dying from breast cancer without first experiencing a distant recurrence.
	  ○ The same approach of assuming general population mortality for patients in the local recurrence health state after 90 days was taken in the recent pertuzumab appraisal (trial death used until 90 days).
	  ○ Non-cancer mortality during the ExteNET trial was lower, not higher, than the UK general population

Technical team judgement after engagement	The technical team agrees with the ERG that extrapolation based on the stratified generalised gamma distribution for iDFS modelling is more plausible than the company's approach as it provided the best overall fit to the data as the proportional hazards assumption is not met. The company's use of general population mortality in the model is appropriate. However, as noted earlier, OS estimates based on iDFS are uncertain.

Issue 4 – Duration and type of treatment effect – for discussion

Background/description of issue	Given the continued treatment effect shown during the trial and the lack of evidence of the treatment effect waning considerably towards the end of the trial**, the company** (CS section B.3.3.1.4 page 98) assumed that the treatment effect observed at the end of the five-year follow-up would be maintained beyond the trial time horizon until patients had equal risk of an iDFS event as the general population (Figure 2). The iDFS 5-year hazard ratio (HR) from the ExteNET label population of 0.58 (95% confidence intervals [CI] 0.41 to 0.82) is applied from year 5 (observed four years after one year of treatment with neratinib) to year 10.75 (129 months) when the hazard rates are switched to the general population rates as the neratinib arm and the general population curves cross and it is implausible for the iDFS rate to be lower than general population rate. The placebo and general population curves cross at year 14.6 (176 months; Figure 2). From month 130 to month 176 (for 3.83 years), the HR increases (on average 0.009 per year) until it becomes one. Implicitly, there is a waning of the treatment effect starting at month 130. In total, 176 months (14.6 years) of neratinib treatment effect are assumed for the base-case (starting from baseline until the time point where placebo and general population mortality hazards are the same). A scenario, assuming a more rapid waning of treatment effect was explored by the company. It was assumed a tapering of the treatment effect over a period of 8.65 years after the end of the trial (from month 63 to month 166). This scenario increased the company base-case incremental cost-effectiveness ratio (ICER) from £24,585 to £31,677 per quality-adjusted life-year (QALY) gain.

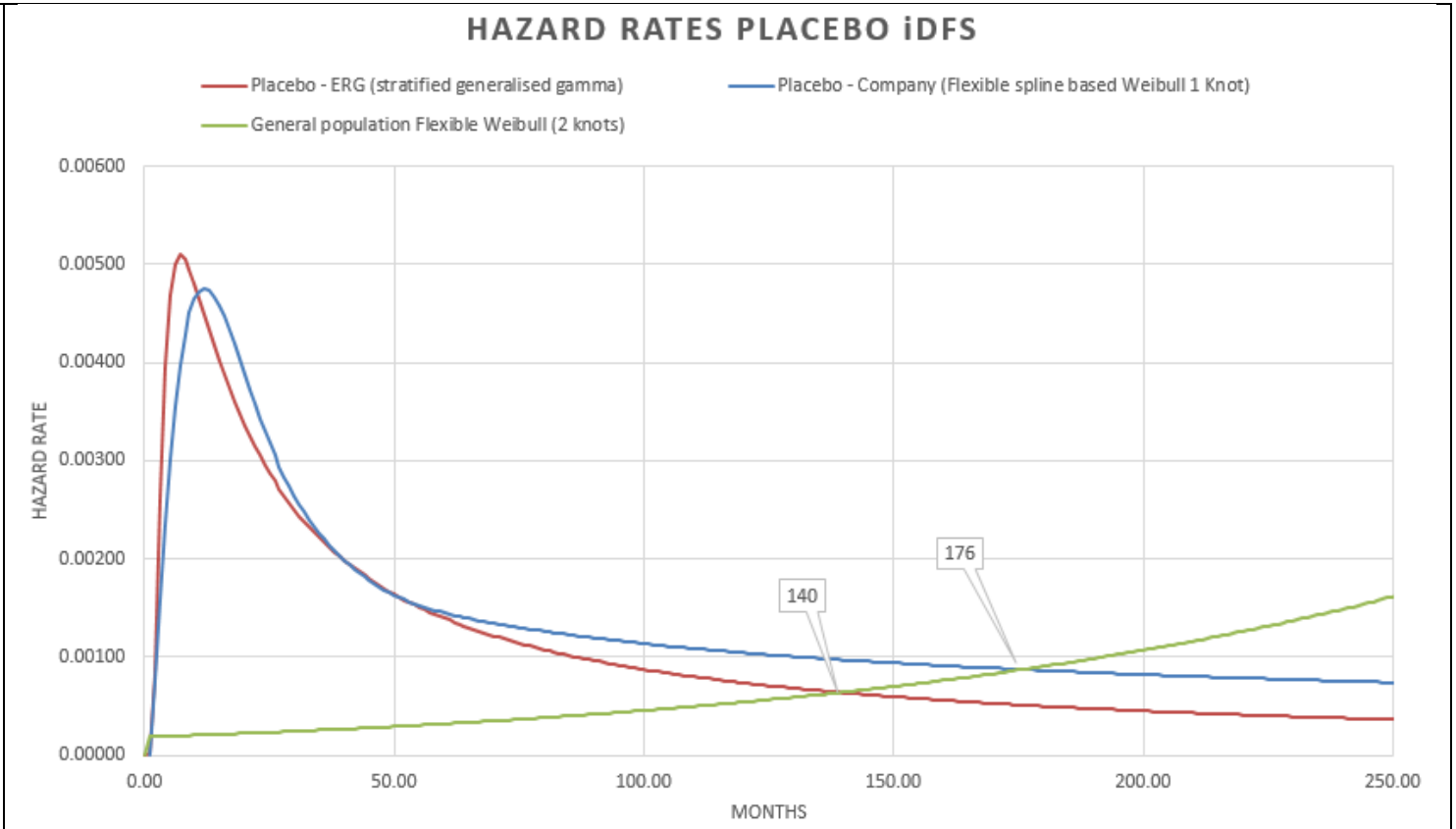

Figure 2 Comparison of hazard rates between the placebo arm iDFS from ExteNET and general population mortality using the company's and ERG's approach to iDFS modelling
Key: iDFS, invasive disease-free survival.
Source: ERG's updated company's model.

The ERG explained that as can be seen in Figure 2 the switching points differ based on the model used to extrapolate iDFS. It seems reasonable to assume that the duration of the neratinib treatment effect is longer

	than five years (starting from baseline) and that it is stops before the time point where placebo and general population mortality hazards are the same. In TA569, it was assumed that the risk of an iDFS event at the end of the trial (4 years) was similar to that of the UK general population and tapering of the treatment effect was implemented from 4 years, with all treatment effect being nullified at 7 years (totalling tapering effect of 3 years duration). Using the ERG's preferred method to extrapolate iDFS (stratified generalised gamma; see Issue 3 – Invasive disease-free survival modelling) the curves crossed at 140 months (11.67 years; the total treatment duration). The ERG applied a tapering effect of 77.2 months duration (140 months minus the total follow-up time in ExteNET of 62.98 months). The ERG incorporated this treatment effect tapering in its preferred base-case and conducted a number of sensitivity analyses (for example using the same approach as the company or assuming shorter taper periods; ERG report table 7.5). **The technical team** is concerned about the treatment effect assumption and although it prefers the ERG's approach of a taper period of 77.02 months (6.42 years), starting at the end of ExteNET follow-up (62.98 months/~5 years) and stopping when the hazard rates in the ExteNET placebo arm crossed the general mortality at 140 months, it notes that this is 3.4 years longer than taper period assumed in TA569.
Why this issue is important	Neratinib's treatment effect duration has a moderate impact on the cost-effectiveness results.
Technical team judgement before engagement	The technical team incorporated the ERG's approach in Table 1: Impact of key issues assumptions on the cost-effectiveness estimate. However, it considers that this may underestimate the resulting ICERs.

Summary of comments	**Comments received from sponsor company Pierre Fabre:**
	
	• Pierre Fabre is willing to accept the ERG's assumption of a tapering of treatment effect for neratinib of 6.4 years, starting after the ExteNET trial, and consider this a conservative assumption:
	  ○ patients with HER2+/oestrogen receptor-positive (ER+) tumours tend to experience recurrence later than those with ER– tumours; therefore, a long treatment effect would be expected in the label population for neratinib.
	  ○ the hazard of recurrence was higher for patients with ER+ disease compared with patients with ER– disease after 5 years (5 10 years: 5.4% vs. 3.3%; 10 15 years: 2.9% vs. 1.3%; 15 20 years: 2.8% vs. 1.2%; and 20 25 years: 1.3% vs. 1.4%; P < 0.001; HER2 status unknown).

	○ Neratinib's intracellular mode of action simultaneously blocks multiple ErbB receptors and has demonstrated inhibition of bidirectional crosstalk between HER2 and ERs that contributes to drug resistance to both HER2-directed agents and endocrine therapy, something that has not been shown with trastuzumab-based regimens and is likely to increase the treatment effect of neratinib. ○ Neratinib and pertuzumab have different modes of action; thus, their treatment effect patterns would not necessarily be the same; the numerically better results for neratinib could be seen as supporting this ○ The ExteNET trial provides an additional year of follow-up (5 years) compared with the clinical data for pertuzumab. There is no evidence to suggest the hazard rate would significantly increase towards the end of the ExteNET trial, which contradicts the applicability of a rapid waning of treatment effect for neratinib. On this basis, the rapid waning effect applied in the pertuzumab model should not be applied to the neratinib model. **Comments received from a clinician expert:** • The ERG's approach to treatment effect tapering is plausible.
Technical team judgement after engagement	The ERG's assumption of a tapering of treatment effect for neratinib of 6.4 years, starting after the ExteNET trial is appropriate for decision making.

Issue 5 –Treatment duration and dose intensity - agreed

Background/description of issue	Neratinib *'is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy'.* The posology section 4.2 specifies that neratinib is used for one year: '*The recommended dose of Nerlynx is 240 mg (six 40 mg tablets) taken orally once daily, continuously for one year* ' In ExteNET the treatment duration per protocol was 1 year and the mean treatment duration reported in the trial was [redacted] months and the median duration was 11.6 months. **The company** (CS section B.3.5.1.1) based neratinib's treatment duration on the mean treatment duration reported in ExteNET ([redacted] months). Similarly, the neratinib dose was based on the relative actual dose intensity from ExteNET ([redacted]%;). **The ERG** (ERG report section 5.2.9) has concerns surrounding the calculation of the treatment duration and the relative actual dose intensity used in the model and the impact this has on the treatment costs. In the CONTROL trial, where prophylaxis was mandated alongside neratinib, diarrhoea related dose holds and dose reductions were lower than in ExteNET trial, where prophylaxis was not mandated. Therefore, the ERG considers that the value for relative actual dose intensity ([redacted]%) and the resulting treatment cost incorporated into the company's base-case are likely to be lower than would be observed in clinical practice, if prophylaxis with loperamide was used routinely. Since the exact dose intensity is unknown, the ERG halved the difference between the ExteNET dose to a full dose (100%) and included the resulting dose intensity of [redacted]% in its preferred base-case. Table A summarises neratinib treatment-emergent diarrhoea in ExteNET and CONTROL trials. **The technical team** is concerned that the treatment duration and dose intensity based on the ExteNET trial could underestimate the cost-effectiveness results.

Table A Neratinib treatment-emergent diarrhoea in ExteNET and CONTROL trials

Neratinib % (n/N)	ExteNET		CONTROL - Loperamide prophylaxis cohort[b]
	Safety population	Label population	
Treatment duration, median/mean	11.6/[redacted] months	NR	11.5/[redacted] months
Relative actual dose intensity median/mean	[redacted]%[a]	NR	[redacted]%
TEAE leading to treatment discontinuation	27.6 (388/1,408)	26.9 (178/662)	[redacted]
Diarrhoea leading to			
• **treatment discontinuation**	16.8 (237/1,408)	16.2 (107/662)	20.4 (28/137)
• **dose reduction**	26.4 (372/1,408)	25.5 (169/662)	7.3 (10/137)
• **dose hold**	33.9 (477/1,408)	NR	15.3 (21/137)
• **hospitalisation**	1.4 (20/1,408)	1.2 (8/662)	1.5 (2/137)
Grade 1-2 diarrhoea	55 (781/1,408)	55.1 (365/662)	48.9 (67/137)
Grade 3 diarrhoea	40 (561/1,408)	39.4 (261/662)	30.7 (42/137)
Cumulative diarrhoea duration: Any grade/Grade ≥ 2/Grade ≥ 3[c]	59/10/5 days	NR	14/5/3 days
Episodes per patient: Any grade/Grade ≥ 2/Grade ≥ 3[c]	8/3/2 episodes	NR	2/2/1 episodes

Key: TEAE, treatment emergent adverse events.
Notes: a, the mean dose reported in CSR was [redacted] and the mean dose reported in CS was [redacted] b, based on an interim analysis; c, one Grade 4 event was reported in neratinib arm in the ExteNET safety population.
Source: Tables 19-25 and Figure 25 in CS, CONTROL CSR interim safety report, and ExteNET CSR.

Why this issue is important	Treatment duration and dose intensity assumptions have a large impact on the cost effectiveness results.

Technical report template 2 – AFTER technical engagement

Technical team judgement before engagement	The technical team incorporated the ERG's approach in Table 1: Impact of key issues assumptions on the cost-effectiveness estimate. However, it considers that this may underestimate the resulting ICERs.
Summary of comments	**Comments received from sponsor company Pierre Fabre:** • Pierre Fabre acknowledges uncertainty around the impact of antidiarrhoeal prophylaxis on dose received and how this will impact on cost. However, if the dose intensity or duration is increased, the efficacy will also improve, and it would be inappropriate to adjust the costs without also adjusting the efficacy. Any adjustments to both costs and efficacy would add further uncertainty because any adjustment would be based on assumptions. • The approach that minimises uncertainty is to assume the dose intensity and duration from the ExteNET trial. **Comments received from a clinician expert:** • It is possible that the tolerable dose and dose duration of neratinib may be higher where diarrhoea prophylaxis is used, however this is difficult to quantify. **ERG:** • Agrees with the company that there is uncertainty surrounding the impact of an increase in dose intensity or duration on efficacy following prophylaxis. While the efficacy may increase, we cannot be sure and there may be additional impact on AE profiles. The ERG considered the adjustment of costs to reflect likely increase in dose intensity in clinical practice to be a conservative assumption. • To avoid additional uncertainty, the ERG have removed the assumption of increased dose intensity from the ERG base-case. This change has a small impact on the ICER.
Technical team judgement after engagement	Neratinib dose and duration based on ExteNET are appropriate for decision making. However, as no diarrhoea prophylaxis was used in ExteNET, there is uncertainty around the impact of anti-diarrhoeal prophylaxis on neratinib clinical and cost-effectiveness.

Issue 6 –Utilities used in the model - agreed

Background/description of issue	**The company** (CS section B.3.4.5) collected EQ-5D-3L in ExteNET at baseline and at month 1, 3, 6, 9, and 12 (end of treatment) for all patients on treatment (regardless of the treatment arm). A protocol amendment (October 2011) removed the requirement for EQ-5D-3L data collection, although originally it was planned to estimate utility values for each of the health states in the model. Mixed models were used to calculate only the utility value for the disease-free state (0.837). The utility value (see glossary for definition of utility value) for the remission health state was assumed to be equal to the disease-free state as in TA569, and Lloyd et al. 2006 was used for distant recurrence and Lindgren at al. 2007 for local recurrence (Table B). A scenario using Lidgren et al. 2007 for all states was also performed. **The ERG** (ERG report 5.2.8 page 83) used ExteNET utilities for iDFS and remission and Lidgren et al. 2007 for the remaining states (Table B). This is similar to the utilities considered by the company in a scenario analysis performed to remove a potential effects of mixing data sources. The ERG has a preference for Lidgren et al. 2007 as it collected EQ5D-3L, while Lloyd et al. 2006 used value vignettes based on an expert opinion. This change has a small effect on cost-effectiveness results. Applying the company's base-case utilities to the ERG's preferred base-case decreased the ERG's ICER of £46,298 per QALY gained to £43,848 per QALYs gained. However, the ERG has limited confidence in relying on the use of this utility value for disease-free state due to a large number of missing data (that have assumed to be missing at random) in the disease-free state utility estimation. And highlighted that, all QALY gains in the model are from the disease-free state. Additionally, assumptions surrounding the disease-free health state utility value have the largest impact on the ICERs in the ERG's deterministic analyses and the third largest impact in the company's deterministic analyses. In addition, the company did not include age-related utility decrements in the model, despite reporting an indication of changes in utility over time. However, since the overall utility of the general population is expected to decrease over time, the ERG incorporated age-based decline in utilities from Janssen and Szende 2014 in the economic analysis.

Table B. Utilities in company's base-case and a scenario analysis, and the ERG's base-case

Heath state	Company's base-case (source)	Company's Lidgren et al. 2007 scenario	Utilities in ERG's preferred base-case (source)
Disease free	**0.837 (ExteNET)**	**0.779**	**0.837 (ExteNET)**
Local recurrence	0.696 (Lidgren et al. 2007)	0.696	0.696 (Lidgren et al. 2007)
Remission (assumed equal to disease free)	0.837 (=disease free)	0.779	0.837 (=disease free)
Distant recurrence < 12 mts	0.521 (Lloyd et al. 2006)	0.685	0.685 (Lidgren et al. 2007)
Distant recurrence > 12 mts		0.685	

Key: CS, company submission; mts, months.
Source: Based on Table 39 in CS.

The technical team agrees with the ERG, that using Lidgren et al. 2007 is more appropriate, although notes that, Lloyd et al. 2006 has been used in previous appraisals. They further note that age-adjusted utilities were also adopted in TA569. Including age-adjusted utilities in the model has a moderate effect on the cost-effectiveness results.

For comparison, utilities used in TA569 are summarised below in Table C.

The technical team would like to know if using the ExteNET utility for disease-free state of 0.837 is appropriate because the values reported in Lidgren et al.2007 and in TA569 are lower.

Table C. Utilities in TA569

Health state		Company's base-case	Source	Lidgren et al. scenario
Non-metastatic	iDFS on chemotherapy	0.756	APHINITY	0.696
	iDFS on treatment/off chemotherapy	0.785		0.696
	iDFS off treatment	**0.822**		**0.779**
	Locoregional recurrence	0.756	= iDFS on chemotherapy	0.779
	Remission	0.822	= iDFS off treatment	0.779
Metastatic	First-line metastatic breast cancer	0.773	Lloyd et al. 2006	0.685
	Second+ line metastatic breast cancer	0.520		0.696

Key: iDFS, invasive disease-free survival.
Source: Based on ERG report for TA569 section 5.2.7.

Why this issue is important	Deterministic sensitivity analyses showed that the utility value for the disease-free state had the largest effect on the resulting ICERs in the ERG's preferred base-case.
Technical team judgement before engagement	The technical team based its analyses on the ExteNET value of 0.837 for disease-free state and remission, and Lidgren et al. 2007 for the remaining states, and adopted the age-adjusted utilities (same as the ERG's preferred analysis). However, it is concerned that the true utility value for disease-free state could be lower than 0.837.
Summary of comments	**Comments received from sponsor company Pierre Fabre:** • Adopted age-adjusted utilities in its updated base-case. • It is most appropriate to use the ExteNET utilities because these meet the NICE reference case, unlike other published utility values that are either in a different population or not based on the EQ-5D.

	• For health states for which utilities cannot be derived from the ExteNET trial, the Lidgren et al. (2007) rates are appropriate to use.
Technical team judgement after engagement	Age-adjusted utilities, ExteNET value for disease-free state, and Lindgren et al. 2007 value for distant recurrence are suitable for decision making. However, the concerns about the utility value for disease-free state due to being estimated with large numbers of missing data remain.

Issue 7 – Outstanding issues

Background/description of issue	This technical report lists all key issue (Issue 1 – The treatment pathway to Issue 6 –Utilities used in the model) and clinical opinion would be valued on these issues. Further outstanding issues are listed in **Error! Not a valid result for table.** and issues that were resolved are listed in **Error! Not a valid result for table.** below.
Why this issue is important	To understand the uncertainty of the cost-effectiveness estimates presented in this report all key sources of uncertainty needs to be identified.
Technical team judgement before engagement	**The technical team** would welcome any additional comments relevant to this appraisal.

Summary of comments	**Comments received from sponsor company Pierre Fabre:**
	• The clinical trial evidence in ExteNET trial is immature. The final OS analysis is expected in [redacted] for the full trial population and in [redacted] for the label population.
	  ○ The two different dates are due to the fact that the timing of the analysis is event driven. Sufficient events will not have occurred in the HR+, within 1 year of trastuzumab subpopulation (EU indication), to allow meaningful comparison between arms until [redacted], as per the existing protocol.
	  ○ Exploratory analysis may be possible, to assess OS events within other patient subgroups (including HR+, within 1 year of trastuzumab
	• It is important to note that, in the EU label analysis, 236 patients (35.2%) in the neratinib arm and 264 (39.8%) in the placebo arm were from the region “Western Europe, Australia and South Africa” and are likely to be similar to the UK population.

Technical team scientific judgement after engagement	No action needed. Table 2 of this report was updated with the information about the final OS analysis and the ExteNET population information.

2. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the Technical Report comments table provided.

Table 1: Impact of key issues assumptions on the cost-effectiveness estimate

Alteration	Notes	PAS ICER
Company post TE base case	**What is new: age-adjusted utilities applied**	[redacted]
1. Lidgren et al. 2007 utility for distant recurrence state instead of Lloyd et al. 2006	Issue 6 –Utilities used in the model	[redacted]
2. Using stratified generalised gamma to model iDFS instead of flexible-spline Weibull with 1 knot	Issue 3 – Invasive disease-free survival modelling	[redacted]
3. Declining treatment effect at 140 months (11.67 years) instead of 166.8 moths (13.9 years).	Issue 4 – Duration and type of treatment effect	[redacted]
Cumulative impact of 1-3 assumptions (ERG's post TE base case)	**What is new: ExteNET neratinib dose ([redacted]; same as company)**	[redacted]

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
ExteNET and the label population	ExteNET (n=2,840) is a phase 3 placebo-controlled randomised controlled trial that compared neratinib treatment with placebo in women aged 18 years or older (≥20 years in Japan) with HER2-positive breast cancer who had completed adjuvant trastuzumab therapy within 2 years. The company submission is based on the label population (that matches neratinib marketing authorisation [n=1,334]; women with early hormone receptor-positive, HER2-positive breast cancer, who have completed a course of adjuvant trastuzumab <1 year ago). Subgroups results should be interpreted with caution. ExteNET was not designed to have statistical power to detect differences between treatments within subgroups.	Unknown.

ExteNET generalisibility	Only 80 patients at 13 sites in the UK were recruited overall, and only 41 (19 in the neratinib arm and 22 in the placebo arm) of these were in the label population (n=1,334). However, 236 patients (35.2%) in the neratinib arm and 264 (39.8%) in the placebo arm were from the region "Western Europe, Australia and South Africa" and were by the company considered likely to be similar to the UK population. In addition, differences by geographical region were reported. Forest plot of five-year invasive disease free survival (iDFS) in hormone receptor-positive participants who had prior adjuvant trastuzumab ≤ 1 year (n=1334) showed that iDFS is statistically significantly in favour of neratinib compared to placebo in North American (n=442) participants (HR 0.48, 95% CI 0.24 to 0.93) but not in West European (n=500) participants (HR 0.70, 95% CI 0.41 to 1.16) or Asian (n=392) participants (HR 0.55, 95% CI 0.29 to 1.02). Subgroups results should be interpreted with caution. ExteNET was not designed to have statistical power to detect differences between treatments within subgroups.	Unknown
ExteNET and immature overall survival (OS)	OS data for the intention to treat (ITT) and the label population (relevant to the decision problem) by treatment arm are not available. The final ITT analysis will be conducted when 248 events have been reported. At the time of the 5-year analysis, only 121 deaths had been reported across both treatment groups combined in the ITT population. Similarly, OS data for the label population remained blinded and are reported for the combined population only. The final OS analysis is expected in [redacted] for the ITT population and in [redacted] for the label population. The two different dates are due to the fact that the timing of the analyses is event driven.	Unknown. However, for a related issue of extrapolating of a surrogate measure for OS see Issue 3 – Invasive disease-free survival modelling.

Adverse events (AEs): The incidence and mean number of events of diarrhoea with prophylaxis using loperamide.	The incidence and mean number of events of diarrhoea with prophylaxis using loperamide was obtained from the safety population of CONTROL trial. CONTROL trial is an ongoing (estimated enrolment=750), phase 2 open-label, safety and tolerability study investigating the effect of anti-diarrhoeal strategies (loperamide, loperamide plus budesonide, and loperamide plus colestipol prophylaxis) on the incidence of neratinib-associated diarrhoea in early-stage HER2-positive breast cancer patients, who have previously undergone a course of trastuzumab therapy in the adjuvant setting. This population does not match the ExteNET label population in terms of length of time from trastuzumab or hormon receptor status.	Unknown.
Subsequent treatments following recurrence	In the company base-case, the cost of distant recurrence was assumed to be £175,390. This value was taken from the TA569 appraisal. Treatments and treatment shares identified through expert elicitation differed somewhat from those obtained from TA569. In the clarification stage the ERG requested that the values from expert elicitation be incorporated into an alternative scenario in the model. The company declined and therefore alternative values have been explored in scenario analyses. When the cost of distant recurrence was increased to £200,000, the ICER was reduced by £2,376 to £43,922 per QALY gained. When the cost of distant recurrence was decreased to £150,000, the ICER was increased by £2,452 to £48,750 per QALY gained.	Unknown. The company's approach was kept in the ERG's preferred analysis and was also used in Table 1: Impact of key issues assumptions on the cost-effectiveness estimate.

Deterministic sensitivity analyses	Deterministic sensitivity analyses were calculated using +/- 10 % of the model values, instead of using 95% Confidence Intervals.	Unknown.

Note: ICERs in this table are taken from the company submission and the ERG report. They were calculated using neratinib list price and are not corrected for the minor error identified post-engagement.

Table 3: Other issues for information

Issue	Comments
Implementation of company model	The ERG highlighted a number of errors in the company model (relating to negative transition probabilities and duration of adverse events). Correction of these errors increased the ICER by £316 per QALY gained.
Transition probability from remission to distant recurrence	In the company base-case, the probability of transition from the remission health state to the distant recurrence health state was fixed and equal to 0.757% as in TA569. Since no other sources of evidence to inform this parameter were available, the ERG assessed the impact of changing this probability on the model results. Halving the transition probability resulted in the ICER increasing by £7,727 per QALY gained. When the transition probability was doubled the ICER decreased by £5,585 per QALY gained. • The company's approach was kept in the ERG's preferred analysis and was also used in Table 1: Impact of key issues assumptions on the cost-effectiveness estimate.
Proportions of patients with local recurrence	In the company base-case, the proportions of patients with local recurrence are based on data from ExteNET (18% for neratinib, and 31% for placebo). The ERG explored + and – 5% changes in proportions for each arm. In the neratinib group, the change to 13% increased the ICER by £2,704 per QALY/gain, and to 23% decreased the ICER by £2,132 per QALY/gain. In the placebo group, the change to 26% decreased the ICER by £3,666 per QALY/gain, and to 36% increased the ICER by £4,703 per QALY/gain. • The company's approach was kept in the ERG's preferred analysis and was also used in Table 1: Impact of key issues assumptions on the cost-effectiveness estimate .

Post distant recurrence survival (PDRS)	In the base-case, a Gompertz distribution was assumed to model PDRS. The fit seems poor in general and based on the AIC and BIC values. The ERG explored three additional scenarios assuming an exponential, a gamma and a Weibull distribution for modelling PDRS. The choice of the parametric distribution for PDRS has a minor impact on the ICER, which at most increased by £2,117 per QALY gained compared to the ERG base-case. • The company's approach was kept in the ERG's preferred analysis and was also used in Table 1: Impact of key issues assumptions on the cost-effectiveness estimate
Innovation	No evidence has been presented on benefits not captured in the measurement of the QALYs and the resulting cost-effectiveness estimates.
End of life considerations	The company did not consider neratinib to be an end of life treatment.
Cancer Drug Fund	The company has not expressed an interest in neratinib being considered for funding through the Cancer Drugs Fund.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

Note: ICERs in this table are taken from the company submission and the ERG report. They were calculated using neratinib list price and are not corrected for the minor error identified post-engagement.

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Appendix

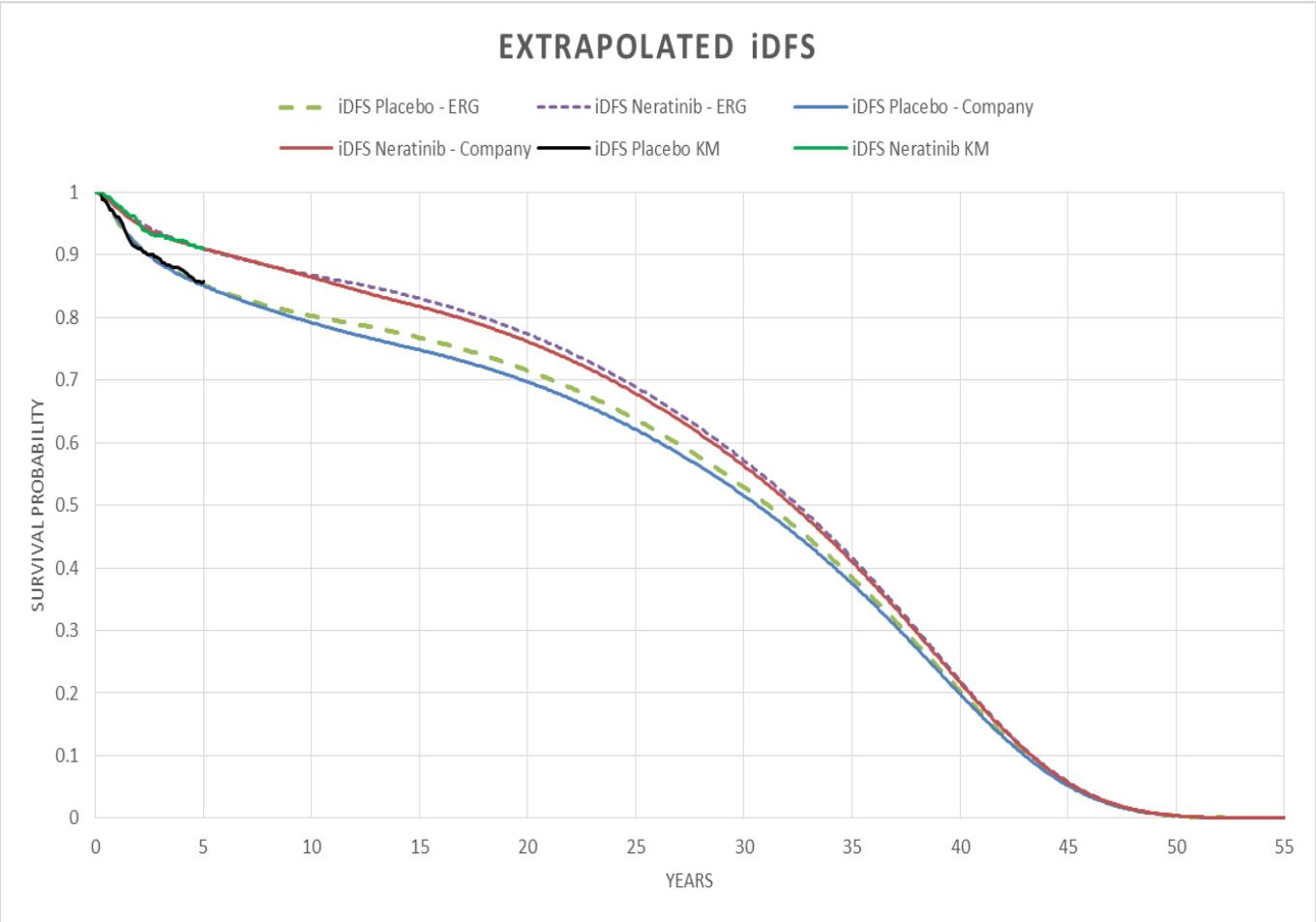

Figure 3 ERG's (stratified generalised Gamma for iDFS & flexible-spline Weibull with 2 knots to model general population mortality) and company's (flexible-spline Weibull with 1 knot to model iDFS & Weibull with 2 knots, to model general population mortality)

Key: iDFS, invasive disease-free survival
Source: ERG's updated company's model. Kaplan-Meier data estimated by digitizing (using WebPlotDigitizer) the Kaplan-Meier curves presented by the company in Figure 6 of the CS.

List of abbreviations

AEs, adverse events

DCIS, ductal carcinoma in situ

DDFS, Distant disease-free survival

DFS, disease-free survival

DFS-DCIS, disease-free survival including ductal carcinoma in situ

EQ5D-3L, European Quality of Life-5-dimension-3 levels questionnaire

ERG, evidence review group

iDFS, invasive disease-free survival

ICERs, incremental cost-effectiveness ratio

PFS, progression free survival

OS, overall survival

PDRS, post distant recurrence survival

QALY, quality adjusted life years

TTD, time-to-treatment discontinuation

Glossary

Quality-adjusted life year (QALY): An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs incorporate changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social, and other factors) of life. Used to measure benefits in cost–utility analysis.

Surrogacy, progression-free survival or disease free survival as a surrogate outcome for overall survival: It may not be possible to obtain a precise estimate of the difference in median overall survival between 2 treatments based on data from a trial where participants have only been followed up for a relatively short time (in particular where <50% of patients have died). Progression-free survival (PFS) or disease-free survival (DFS) is a surrogate outcome for overall survival (OS) if a gain in PFS/DFS comparing 1 treatment with another can be assumed to translate to an equivalent gain in OS. Partial surrogacy would imply that the gain in OS is a certain percentage of the gain in PFS/DFS.

Systematic review: Research that summarises the evidence on a clearly formulated question according to a predefined protocol. Systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings are used. Statistical methods for meta-analysis may or may not be appropriate for application to the quantitative results from the different studies.

Utility: A measure of the strength of a person's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.