CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Neratinib (Nerlynx) for Early Breast Cancer

December 5, 2019

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List of Abbreviations

AE(s)	Adverse events
aITT	Amended intention-to-treat
CBCN	Canadian Breast Cancer Network
CORD	Canadian Organization for Rare Diseases
CGP	Clinical Guidance Panel
CI	Confidence interval
CTCAE	Common Terminology Criteria for AEs
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DDFS	Distant disease-free survival
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQOL 5 Dimensions Questionnaire
EMA	European Medicines Agency
ExteNET	Extended adjuvant treatment of breast cancer with neratinib
FACT-B/G	Functional Assessment of Cancer Therapy - Breast/General
GI	Gastrointestinal
HR	Hormone receptor
HER2	Human epidermal growth factor receptor 2
HRQoL	Health-related quality of life
IDFS	Invasive disease-free survival
ITT	Intent-to-treat
K-M	Kaplan-Meier
MCID	Minimal clinically important difference
MEDRA	Medical Dictionary for Regulatory Activities
OS	Overall survival
PAG	Provincial Advisory Group
pCODR	pan-Canadian Oncology Drug Review
pCR	Pathological complete response
pERC	pCODR Expert Review Committee
RCT	Randomized controlled trial
SAEs	Serious adverse events
SAP	Statistical analysis plan
SD	Standard deviation
TTDR	Time-to-distant recurrence
T-DM1	Trastuzumab emtansine
STEEP	Standardized definitions for efficacy endpoints in adjuvant breast cancer trials

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding neratinib in early stage breast cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding neratinib for early stage breast cancer conducted by the Breast Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group (PAG); input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7, respectively. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on neratinib for early breast cancer, a summary of submitted Provincial Advisory Group Input on neratinib for early breast cancer, and a summary of submitted Registered Clinician Input on neratinib for early breast cancer, and are provided in Sections 2, 3, 4, and 5, respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of neratinib as monotherapy for the extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor 2 (HER2)-positive, hormone-receptor (HR)-positive breast cancer who have completed adjuvant trastuzumab-based therapy within the past year.

Health Canada issued a Notice of Compliance (NOC) for neratinib (Nerlynx) for the extended adjuvant treatment of women with early-stage HR-positive, HER2-overexpressed/amplified breast cancer within one year after completion of trastuzumab-based adjuvant therapy. The funding request under review by pCODR aligns with the patients described in the Health Canada indication.

Neratinib is a protein kinase inhibitor that irreversibly binds to Epidermal Growth Factor Receptor (EGFR), HER2, and HER4. The recommended dose is 240 mg (six 40mg tablets) given orally once daily with food, continuously for one year at approximately the same time every day.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One randomized controlled trial (RCT), ExteNET, met the inclusion criteria of the pCODR systematic review.

ExteNET (Extended Adjuvant Treatment of Breast Cancer with Neratinib) [2,3]

ExteNET is a multicentre, randomized, double-blind, placebo-controlled, phase III trial that was conducted at 495 centres in Europe, Asia, Australia, New Zealand, and North and South America and included 93 patients from 14 Canadian centres. The aim of the trial was to evaluate the efficacy and safety of 12 months of neratinib treatment following

trastuzumab-based adjuvant therapy in patients with early-stage HER2-positive breast cancer. The sponsor has requested reimbursement for a subgroup of the ExteNET trial population: patients with HR-positive breast cancer who completed trastuzumab treatment within the past year.

The trial consisted of three parts: a primary analysis period of 2 years (part A), an extended follow-up of 3-5 years (part B), and long-term follow-up of overall survival (OS) (part C). Patients were randomized to receive oral neratinib 240 mg (6X40 mg tablets/day) or placebo daily for up to 12 months (or until toxicity develops) in a 1: 1 ratio; stratified by HR status, nodal status, and trastuzumab adjuvant regimen. Patients, investigators, and trial sponsors were masked to treatment allocation during the 2-year primary analysis period, following which a firewall was established to prevent all study personnel to have access to the study data.

Eligible patients were ≥ 18 years of age (≥ 20 in Japan), had confirmed stage I–III HER2-positive breast cancer (later amended to be stage II-III) without evidence of recurrence, known HR status, completed neoadjuvant and adjuvant trastuzumab therapy up to 2 years before randomization (later amended to 1 year), and had no other significant comorbidities that would preclude them from participation. Patients who received prior neoadjuvant therapy were eligible; however, those who achieved a pathologic complete response (pCR) or ductal carcinoma *in situ* (DCIS) and axillary pCR following neoadjuvant therapy were excluded from the trial, as were those who received prior HER2-directed therapy other than trastuzumab.

The primary efficacy endpoint was invasive disease-free survival (IDFS) at 2 years, defined as the time from randomization to the first occurrence of invasive ipsilateral breast tumour recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause. Additionally, DFS including ductal carcinoma in situ (DFS-DCIS), distant disease-free survival (DDFS), time-to-distant recurrence (TTDR), incidence of central nervous system (CNS) recurrence, and overall survival (OS) were measured as secondary efficacy endpoints. Health-related quality of life (HRQoL) was an exploratory endpoint, measured using the Functional Assessment of Cancer Therapy - Breast (FACT-B) and EuroQoL-5D (EQ-5D) scales. All endpoints were analyzed at 2 and 5 years, except for HRQoL measures, which were analyzed at 12 months. The final analysis for OS is planned for when 248 OS events are observed. With the exception of OS, none of the secondary endpoints were analyzed with adjustment of type-1 error for multiplicity; and none of the subgroup analyses, including the target subgroup relevant for this review, were controlled for multiplicity.

The trial protocol had several amendments resulting from multiple changes in trial sponsor that affected the original study design. These included three notable amendments related to eligibility criteria, sample size, and study length. The first of these amendments changed the eligibility criteria to include more high-risk patients (stage II-III, node-positive, who completed trastuzumab ≤ 1 year before randomization), reducing the required sample size, with primary analysis to be performed in this enriched population (termed amended intent-to-treat [ITT] or aITT population). A later amendment stopped further recruitment of patients and truncated the follow-up duration from 5 years to 2 years, further reducing the required sample size. The final protocol amendment restored the original primary analysis, i.e. 2-year IDFS in the ITT population (which included both low- and high-risk patients). Additionally, the follow-up was restored to 5 years (or longer for OS), and patients were required to re-consent to extended follow-up. Notably, data from year 3-5 were collected retrospectively, with fewer patients available due to loss to follow-up.

A total of 2840 patients were randomized and constituted the ITT population. At the end of the 2-year primary analysis period, a total of 53 patients died and therefore were not available for extended follow-up. Of the remaining 2787 patients, 2117 patients (76%) re-consented to the 5-year extended follow-up. Baseline characteristics were largely similar among the ITT and re-consented population, with no notable imbalances between treatment groups. In the ITT population, the median age was 52.3 years, 59.9% were ≥ 50 years of age, 81% were White, 53.3% were post-menopausal, 46.8% had 1-3 positive nodes, 57.4% were HR-positive, 70% had stage II-III tumours, 47.3% had poorly differentiated histology, and 94% had ductal carcinoma. In terms of prior anti-cancer therapy, the majority of patients had received prior radiotherapy and chemotherapy and received adjuvant trastuzumab within 1 year from randomization. The distribution of baseline characteristics was similar in the target subgroup of interest for this review - patients with HR-positive breast cancer who completed trastuzumab within the past year.

Strengths of the trial included appropriate methods for randomization, blinded treatment allocation, outcome assessment, and statistical analysis. However, several limitations were identified that should be considered when interpreting the results.

- The trial protocol was amended several times; however, these changes were based on external information and therefore unlikely to have an impact on the control of type-1 error rate.
- It should be noted that all efficacy analyses, except for 2-year IDFS (and OS when data mature), were not adjusted for multiplicity; therefore, results of the secondary outcomes and subgroup analyses (including the subgroup for which funding request is sought) should be interpreted with caution. Additionally, analysis of the target subgroup was not pre-specified in the trial protocol/SAP and was performed *post-hoc* and therefore may not be adequately powered resulting from a smaller subset of the ITT population – two factors that increase the uncertainty of the results.
- The number of patients who discontinued treatment and the trial at 2 years was higher in the neratinib group compared with placebo. The disproportionate discontinuation/dropout rate was primarily due to adverse events (AEs) and subject request. It is unclear if the disproportionate discontinuation/dropout rate biases the trial results since there is no evidence to suggest the reason for discontinuation/dropout was associated with the outcome.
- A quarter of trial patients did not re-consent for the extended 5-year follow-up and fewer patients in the neratinib group provided re-consent for the extended follow-up. Results in this population are therefore, in part, affected by immortal time bias. However, the sponsor indicated the 5-year analyses were done in the ITT population in order to minimize selection bias resulting from excluding non-reconsented patients.
- The high pill burden (6 tablets/day for 12 months) raises a concern as to whether the 100% compliance rate as seen in the trial can be generalized to real-world practice.

Efficacy

The key efficacy outcomes of the ExteNET trial are presented in Table 1.

Primary efficacy endpoint: In the target subgroup relevant for this review (HR-positive patients who completed trastuzumab within the past year), both 2- and 5-year IDFS showed a clinical benefit among neratinib-treated patients. In this subpopulation, the 2-year IDFS rate was 95.3% and 90.8% in the neratinib and placebo groups, respectively (hazard ratio=0.49, 95% CI: 0.30, 0.78; absolute difference of 4.5%). The clinical benefit

of neratinib in this subgroup was consistent at 5-year follow-up (hazard ratio=0.58, 95% CI: 0.41, 0.82; absolute difference 5.1%). Since the subgroup analysis was neither pre-specified nor adjusted for multiplicity, results should be interpreted with caution.

In the ITT population, 67 patients receiving neratinib had an event at 2 years compared with 106 patients receiving placebo; with IDFS rates of 94.2% and 91.9%, respectively (stratified hazard ratio=0.66, 95% CI: 0·49, 0·90; stratified 1-sided p = 0·004). In the re-consented population, 116 patients in the neratinib group and 163 patients in the placebo group had an event at 5 years, with corresponding rates of 90.2% and 87.7%, respectively (hazard ratio=0.73; 95% CI: 0.57, 0.92; stratified 1-sided nominal p = 0.004). Of the IDFS events, distant recurrence constituted the most frequent site of disease recurrence in both groups. OS data are not mature since the target of 248 events has not been reached. At the end of the 5-year follow-up, a total of 121 deaths were reported in both treatment groups combined.

Secondary efficacy endpoints: Analyses of secondary efficacy endpoints at 2 and 5 years showed greater benefits in patients treated with neratinib compared with placebo, both in the target subgroup and the ITT population. In the target subgroup, the hazard ratios for DFS-DCIS, DDFS, and TTDR at 2 years were 0.45, 0.53, and 0.53, respectively; and at 5 years were 0.55, 0.57, and 0.58, respectively (nominal p values < 0.05 for all outcomes and time points). In the ITT population, the hazard ratios for DFS-DCIS, DDFS, and TTDR at 2 years were 0.61, 0.74, and 0.73, respectively; and at 5 years were 0.71, 0.78, and 0.79, respectively (nominal p values < 0.05 in all cases, except for DDFS and TTDR at year 2).

Health-related Quality of Life

Both HRQoL measures, the Functional Assessment of Cancer Therapy - Breast (FACT-B) and the EuroQoL 5-dimensions (EQ-5D), demonstrated an initial decrease in scores in both treatment groups at month 3, with scores gradually increasing close to baseline values by month 12. The decrease was more prominent in the neratinib group and peaked at month 1; however, there was no noticeable between-treatment group differences by month 12. The minimal clinically important difference (MCID) was not reached for either measure at any timepoint. The questionnaire completion rates were generally high, approximately 80% or more; however, the rates decreased to approximately 70% towards the end of the 12-month follow-up period.

Harm Outcomes

The median duration of treatment was approximately 11 months. Overall, more patients in the neratinib group experienced AEs (98.5% versus 88.1%), grade ≥ 3 AEs (49.7% versus 13.1%), serious AEs (SAEs) (7.3% versus 6.0%), AEs leading to treatment discontinuation (27.6% versus 5.4%), dose reduction (31.3% versus 2.5%), and dose hold (44.7% versus 13.3%) compared with the placebo group. Diarrhea (grade 1-3) was the most frequently reported AE among neratinib treated patients compared with placebo (95.3% versus 35.4%). Patients in the neratinib group also reported more grade 1-2 fatigue, vomiting, abdominal pain and upper abdominal pain, rash, decreased appetite, and muscle spasms. Incidences of SAEs were low, and mostly gastrointestinal (GI) or hepatic in nature.

Table 1: Highlights of key outcomes in the ExteNET trial[2,3]

Outcomes	ExteNET	
	Neratinib (N=1420)	Placebo (N=1420)
2-year IDFS, ITT population		
Events, n (%)	67 (4.7)	106 (7.5)
Kaplan-Meier Estimate, 95% CI	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)
Stratified hazard ratio (95%CI)	0.66 (0.49, 0.90)	
p-value (1-sided)	0.004	
5-year IDFS, ITT population		
Events, n (%)	116 (8.2)	163 (11.5)
Kaplan-Meier Estimate, 95% CI	90.2 (88.3, 91.8)	87.7 (85.7, 89.4)
Stratified hazard ratio (95%CI)	0.73 (0.57, 0.92)	
p-value (1-sided)	0.004	
Subgroup: HR-positive, completed trastuzumab ≤1 year	N=670	N=664
2-year IDFS Events, n	26	55
Kaplan-Meier Estimate, 95% CI	95.3 (93.1, 96.7)	90.8 (88.2, 92.9)
Unstratified hazard ratio (95%CI)	0.49 (0.30, 0.78)	
p-value (1-sided)	0.001	
5-year IDFS Events, n	51	89
Kaplan-Meier Estimate, 95% CI	90.8	85.7
Unstratified hazard ratio (95%CI)	0.58 (0.41, 0.82)	
p-value (1-sided)	0.001	
Harms, n (%)	**Neratinib (N=1408)**	**Placebo (N=1408)**
Grade ≥3	700 (49.7)	184 (13.1)
AE (any grade)	1387 (98.5)	1240 (88.1)
TRAE	1353 (96.1)	805 (57.2)
WDAE	388 (27.6)	76 (5.4)

Abbreviations: AE = adverse events; IDFS = Invasive disease-free survival; ITT = intention-to-treat, HR = hormone receptor; TRAE = treatment related AE; WDAE = withdrawal (from treatment) due to AE

1.2.2 Additional Evidence

Refer to Sections 3, 4, and 5 for a complete summary of Patient Advocacy Group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

Two patient advocacy groups, Canadian Breast Cancer Network (CBCN) and the Canadian Organization for Rare Disorders (CORD), provided input on neratinib for early breast cancer. For a summary of this input, refer to Section 3.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) and a federal drug plan participating in pCODR. PAG identified clinical and economic factors that could impact the implementation of neratinib for early breast cancer. For a summary of this input, refer to Section 4.

Registered Clinician Input

Two clinician input submissions, one joint submission and one individual submission, were provided. In total, the input received captured the perspectives of four oncologists from Ontario. For a summary of this input, refer to Section 5.

Summary of Supplemental Questions

No supplemental questions were identified during development of the review.

Comparison with Other Literature

Diarrhea is the main toxicity associated with neratinib as observed in the ExteNET trial. Diarrhea incidence is particularly high in the early course of treatment; therefore, a structured prophylactic regimen is recommended to minimize diarrheal episodes. CONTROL[4] is an open-label, phase II trial, that was initiated to characterize the incidence and severity of diarrhea in patients with early stage HER2-positive breast cancer treated with neratinib and intensive loperamide prophylaxis. Given the prescription of neratinib will likely include a prophylactic agent for diarrhea, the Clinical Guidance Panel (CGP) identified this study as being relevant.

The eligibility criteria in the CONTROL trial were largely similar to the ExteNET trial. Patients received one of three loperamide prophylaxis regimens – loperamide alone (1 or 2 cycles) and in combination with budesonide or colestipol (1 cycle each). Each treatment cycle was four weeks in length, with additional loperamide given as needed after the completion of the treatment schedule. Safety endpoints were primarily assessed in the trial, with a focus on diarrhea. In addition, HRQoL was assessed using the FACT-B and EQ-5D-5L. Comparisons between the treatment cohorts were done descriptively. In addition, the neratinib group of the ExteNET trial, who were not required to receive antidiarrheal prophylaxis, was used as a historical control.

A total of 321 patients were enrolled from 41 sites. The loperamide, budesonide, and colestipol cohort consisted of 137, 64, and 120 patients, respectively. Overall, baseline demographic and clinical characteristics were similar across treatment groups. Approximately 70% of the patients were stage II-III, over 70% had HR-positive tumours, and most patients received trastuzumab and taxanes. Notably, 40% patients in the loperamide cohort received prior pertuzumab, compared with approximately 60% patients in the budesonide and colestipol cohort. As of the data cut-off date, all patients in the loperamide cohort completed or prematurely discontinued neratinib treatment, as opposed to 73% and 21% of patients in the budesonide and colestipol cohorts, respectively; and the median duration of neratinib treatment in the three cohorts was 11.5, 11.9, and 3.7 months, respectively.

In terms of results, all three antidiarrheal prophylaxis regimens in the CONTROL trial reduced diarrheal episodes, duration and severity, and neratinib dose modification due to diarrhea compared with the neratinib group in the ExteNET trial. Additionally, the occurrence and severity of diarrhea over the course of neratinib treatment was markedly reduced in the CONTROL trial compared with the ExteNET trial. Aside from diarrhea, the overall safety profile of neratinib with loperamide prophylaxis given with or without budesonide or colestipol was similar to that reported in the ExteNET trial, with the exception of an increase in constipation in the CONTROL trial.

Within the CONTROL trial, loperamide in combination with colestipol resulted in the lowest incidence of grade ≥ 3 diarrhea (10.8%), followed by loperamide plus budesonide (26.6%), and loperamide alone (30.7%). Loperamide in combination with colestipol also improved the tolerability of neratinib and required fewer dose modifications compared to

the other regimens. However, a comparative conclusion between the antidiarrheal regimens should not be drawn due to the following reasons: the trial was open-label in nature, formal statistical tests were not conducted, and a disproportionate number of patients in the three cohorts completed neratinib treatment as of the data cut-off date, which is the primary cause of diarrhea (21%, 73%, and 100% in the colestipol, budesonide, and loperamide cohort, respectively).

See Section 8 for further details on the CONTROL trial.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence; an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for neratinib for the adjuvant treatment of early breast cancer.

Domain	Factor	Evidence from the ExteNET trial[2,3]	Generalizability Question	CGP Assessment of Generalizability
Population	Prior neoadjuvant therapy	Patients who had prior neoadjuvant therapy were eligible if they had residual invasive cancer in the breast and/or axilla following completion; excluded if they achieved pCR in breast and axilla, or if they have only residual DCIS and pCR in axilla.	Is the decision of including/excluding patients based on prior neoadjuvant therapy aligned with neratinib-eligible patients in Canada?	Patients who had prior neoadjuvant therapy and achieved a pCR or eliminated all invasive disease in the breast and nodes will not be eligible for neratinib. Those patients with residual disease after neoadjuvant chemotherapy would be eligible to receive adjuvant neratinib.
	ECOG Performance Status	The trial limited eligibility to patients with an ECOG performance status of 0-1.	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor etc.)?	Patients after one full year off chemotherapy and solely on trastuzumab will almost all have an ECOG PS of 0 or 1. Patients who do not will largely be those with major comorbid conditions (i.e., ECOG status will not be disease related) and will most likely not be offered neratinib.
	Notable exclusion criteria	Patients were excluded if they had local or regional recurrence, were receiving any concomitant anti-cancer therapy, prior therapy with a HER2 inhibitor other than trastuzumab, a second malignancy, major concurrent or previous illness or medical conditions.	While results may not be directly generalized to these patients, which of these groups, if any, may still be eligible for neratinib in Canadian setting?	Patients who received pertuzumab will largely not be eligible for adjuvant neratinib. Patients who have received adjuvant T-DM1 to treat residual disease in the breast or axilla after neoadjuvant chemotherapy were not included in the ExteNET trial, so the benefit of neratinib in this context is not known. Second malignancy patients were excluded from clinical trials but are largely treated in practice as every other patient unless they have active

Domain	Factor	Evidence from the ExteNET trial[2,3]	Generalizability Question	CGP Assessment of Generalizability
				disease/metastatic disease.
	Baseline characteristics	• The trial enrolled patients aged ≥ 18 years, median 52. Refer to baseline characteristics for age distribution • ~46% patients had 1-3 positive nodes, ~30% with ≥4 positive nodes, and ~23% were node-negative • >50% were postmenopausal • Refer to distribution of tumour stage, histological grade, and primary cell type in baseline characteristics • Patients were randomized within a median of ~4 months following last trastuzumab, which was given for a median of ~11 months	Are the baseline characteristics reflective of Canadian patients who may be eligible for neratinib treatment?	The baseline characteristics of patients in the ExteNET trial are reflective of Canadian patients who may be eligible for neratinib but are likely not characteristic of who will be treated. This is a therapy with a relatively small benefit, and clinicians will likely treat a higher risk subset than was observed in this trial - i.e. those with ≥4 positive nodes. Some clinicians are moving to six months of trastuzumab for low-risk patients, and neratinib would not typically be given to these patients.
Intervention	Pill burden	6 tablets of neratinib is to be taken daily, and median compliance was 100% in the trial	Is this finding applicable to the target population?	The average (mean) compliance would be expected to be less. In general, it would be expected that compliance would be similar.
Outcomes	Appropriateness of primary and secondary outcomes	Primary outcome: IDFS (modified STEEP definition, which excludes second primary non-breast cancers) Secondary outcomes: DFS-DCIS, DDFS, TTDR, CNS recurrence Exploratory outcomes: FACT-B, EQ-5D	Were the primary and secondary outcomes appropriate for the trial design?	IDFS is a reasonable surrogate endpoint for a clinically meaningful outcome in the adjuvant setting. However, follow-up in this trial is short (with a low event rate) and OS data are awaited to confirm clinical benefit.

Abbreviations: CGP = clinical guidance panel; CNS - central nervous system; DCIS = ductal carcinoma in situ; DDFS = distant disease-free survival; EQ-5D = EuroQOL 5 Dimensions Questionnaire; ExteNET = Extended Adjuvant Treatment of Breast Cancer with Neratinib; (I)DFS = (invasive) disease free survival; ECOG = Eastern Cooperative Oncology Group; FACT-B = Functional Assessment of Cancer Therapy - Breast/General; HR = hazard ratio; HER2 = human epidermal

growth factor receptor 2; HR-positive/negative = hormone receptor positive/negative; HR-positive = hormone receptor positive; OS – overall survival; pCR = pathologic complete response; PS – performance status; STEEP = standardized definitions for efficacy endpoints in adjuvant breast cancer trials; TTDR = time-to-distant recurrence

1.2.4 Interpretation

Burden of Illness in Canada

Approximately 26,000 new cases of breast cancer, and 5000 deaths from breast cancer occur each year in Canada. Of new cases, approximately 95% are early stage disease (stage I, II, or III), while 5% present with clinically detectable metastatic disease (stage IV).[5] Of deaths from breast cancer, approximately 75% occur in patients who presented initially with no detectable metastatic disease, but subsequently develop it. HER2-positive early breast cancer occurs in approximately 20% of patients; of these breast cancers, approximately 50% are also HR-positive.

Need

Patients with HER2-positive and HR-positive breast cancer are typically treated with adjuvant or neoadjuvant chemotherapy with trastuzumab-based treatment for one year. In addition, they are treated with hormone therapy such as tamoxifen or an aromatase inhibitor, bone targeted agents, and radiation therapy as needed.[6-8] Although the vast majority of cancers do not relapse, there are several hundred patients per year who die of metastatic HER2-positive, HR-positive breast cancer in Canada. Metastatic HER2-positive breast cancer is considered a lethal condition. Recently, several attempts to improve on the efficacy and/or safety of the standard of care have been published. Pertuzumab, which is also a monoclonal antibody that binds HER2 at a different epitope than trastuzumab, was combined with trastuzumab as an adjuvant treatment. This combination, studied in the APHINITY trial,[9] improved IDFS for patients as a whole, but the improvement in HR-positive disease was notably small, with a 0.4% improvement in IDFS at three years.

A more promising evolving approach has been to combine chemotherapy with targeted therapy, using adjuvant trastuzumab emtansine (T-DM1), which is a standard HER2 targeted antibody conjugated with cytotoxic chemotherapy, in patients who have received neoadjuvant therapy but do not obtain a pCR. Patients who receive neoadjuvant HER2-targeted therapy and have residual disease have a significantly higher risk of breast cancer relapse and death than those who have a pCR. While the standard treatment for this group of patients has been continuation of trastuzumab and hormonal therapy if indicated, the KATHERINE trial[10] compared this standard strategy to adjuvant T-DM1 and demonstrated a lower risk of invasive relapse or death with T-DMI (hazard ratio=0.50; 95% CI: 0.39 to 0.64; $p<0.001$), with 23% of patients in the standard treatment group having an IDFS event at 3 years compared to 11.7% in the T-DM1 group. In HER2-positive and HR-positive patients, the rates of invasive relapse or death were 19.3% and 9.3% in the standard treatment and T-DM1 groups, respectively. Importantly, this trial also included subgroups of patients who are at very high risk, such as those with ypN2 or ypN3 disease.

To address the need to improve on outcomes for patients at a high risk of recurrence following standard trastuzumab therapy, the ExteNET trial examined an extension of anti-HER2 therapy with neratinib,[2,3] which has a different mechanism of HER2 targeting to trastuzumab (or T-DM1), comparing it to no additional therapy after the completion of one year of adjuvant trastuzumab-based therapy, with the hopes of reducing recurrences and ultimately possibly improving either quantity or quality of life. IDFS was chosen as the primary endpoint of the ExteNET trial; this surrogate outcome has shown to have a moderate to strong association with OS in HER2-positive early breast cancer, at least for up-front therapy.[11]

Intervention of Interest and Rationale for Its Use

Neratinib is a small oral molecule pan-HER inhibitor, that acts at the kinase domain of HER1, HER2, and HER4. It has some activity in the single agent setting in trastuzumab pre-treated patients and may help in patients for whom trastuzumab therapy alone is not sufficient due to its ability to act on known resistance pathways to HER2 therapy, including HER1, which is a heterodimerization partner of HER2, and HER4. Extended adjuvant therapy with HER2-targeted therapy with the same mechanism of action – i.e. extended trastuzumab for two years was previously compared to one year of trastuzumab but showed no benefit.[12] Neratinib, a drug with a different mechanism of action, was studied as extended adjuvant therapy in a similar setting to extended trastuzumab.

ExteNET Trial

For the current submission of neratinib, the pCODR Methods Team performed a systematic review and examined the eligible literature evaluating neratinib as extended adjuvant therapy for patients with HER2-positive breast cancer who had completed adjuvant trastuzumab therapy. One trial was found that met the eligibility criteria of the review – the ExteNET trial.[2,3] An additional study – the CONTROL trial,[13] was also reviewed since it provided evidence on prophylactic regimens to manage diarrhea in patients treated with neratinib (refer to Section 8 for a summary of the evidence from the Control trial).

The ExteNET trial randomized patients in a one to one fashion to neratinib or placebo. Randomization was stratified for known prognostic factors, including HR status, node status (N0 versus N1 versus N2 or N3), and type of trastuzumab adjuvant therapy (concurrent or sequential). Patients were randomized at any time after trastuzumab treatment, but this eligibility criterion was amended to within one year of the completion of trastuzumab. Patients were given a starting dose of 240 mg of neratinib daily or matching placebo for one year, with dose reductions to 200 mg/160 mg/120 mg allowed. Patients were able to receive other standard adjuvant treatments such as endocrine therapy. The primary outcome of IDFS was defined as the first occurrence of invasive ipsilateral breast tumour recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause.

Efficacy

At the 2 year data cut-off date (primary efficacy analysis), neratinib provided a statistically significant improvement in IDFS in the ITT patient population with fewer IDFS events (67 versus 106) in the neratinib group compared to placebo (hazard ratio=0.66; 95% CI: 0.49, 0.90, p=0.004), which translated to a 2.3% difference in IDFS rates at 2 years (94.2% versus 91.9% for neratinib and placebo, respectively). The treatment benefit persisted at 5 years follow-up (116 versus 163 IDFS events, respectively; hazard ratio=0.73; 95% CI: 0.57, 0.92, p=0.004) at which point there was a 2.5% difference in IDFS rates (90.2% versus 87.7%, respectively). Distant recurrence constituted the most frequent site of disease recurrence at 5 years occurring in 6.0% of patients in the neratinib group and 8.0% in the placebo group. Data on OS are considered immature and therefore are not currently available.

The Sponsor has requested funding for a patient population that differs from the ITT population studied in the ExteNET trial; specifically, for a subgroup of patients with HR-positive tumours who have completed trastuzumab therapy in the previous year. Based on sensitivity analyses of the ExteNET trial data, the benefit of neratinib appeared greater in this subgroup of patients, with fewer IDFS events in the neratinib group (26 versus 55) compared to placebo (hazard ratio=0.49; 95% CI: 0.30, 0.78), which represents a 51% reduction in the risk of disease recurrence or death and a 4.5% difference (95.3% versus

90.8%, respectively) in IDFS rates at 2 years. A similar benefit was observed at 5 years of follow up (51 versus 89 events, respectively; hazard ratio=0.58; 95% CI: 0.41, 0.82), at which point there was a 5.1% difference in IDFS rates (90.8% versus 85.7%, respectively).

HRQoL was an exploratory endpoint of the trial; and data were reported that showed neratinib was associated with a small reduction in HRQoL during the early stages of therapy but HRQoL appeared to improve and was similar to placebo by 12 months. However, it is unclear to the CGP if this result was due to a waning effect, treatment of the toxicity, or also the effect of patients withdrawing from treatment. In adjuvant treatment, the expectation would be that quality of life with any therapy will be somewhat worse than with no treatment until the treatment is stopped or toxicities are managed. Any HRQoL benefit due to adjuvant therapy, such as extended neratinib, occurs due to a delay in the development of invasive (metastatic or recurrent) disease; unfortunately, this was not assessed in the trial as HRQoL was only evaluated while on treatment with neratinib (12 months).

Safety – Toxicity and Adverse Events

In terms of toxicity, there are several toxicities that occur with neratinib that appear significantly greater than with placebo. Neratinib has substantial GI toxicity that often requires dose adjustments and delays; 40% of patients had grade 3/4 diarrhea with neratinib, 31% of patients required dose reduction, and 28% of patients were required to stop neratinib due to AEs. Although diarrhea appeared to improve over the year of therapy (mean grade of diarrhea was highest on day 4 of neratinib, and then was significantly reduced at the end of the year), it is unclear whether this was the result of selective drop-out of neratinib patients, increased use of antidiarrheal agents, a waning effect/tolerance effect, or all three. Regardless, diarrhea and other GI toxicities are significant with neratinib but do not appear to be long lasting, and appear to be manageable with dose reductions, supportive medications, and cessation of therapy if needed. The CONTROL trial examined the use of prophylactic antidiarrheal drugs in patients receiving adjuvant neratinib[13] and showed a decrease in grade 3 diarrhea from roughly 40% to 30%, suggesting at least prophylaxis may have some benefit, although this difference is difficult to fully interpret given the differences in patient populations (i.e. patients in the CONTROL study may have already been selected out for not having diarrhea, as a significant number had already received pertuzumab plus trastuzumab without diarrhea).

The toxicity most closely associated with HER2 targeted therapies is cardiac toxicity, and neratinib appeared to have a very low rate of cardiac toxicity. These patients are selected to have already tolerated trastuzumab without cardiac events or compromise and were screened prior to trial enrolment, so this is not a surprising result. There was no clear evidence of serious long-term toxicities (cardiotoxicity, second malignancies) but median follow is still relatively short for an adjuvant treatment with high patient survival rates free of breast cancer. In the adjuvant setting treatment-related deaths are extremely concerning, and there did not appear to be any treatment-related deaths with neratinib.

Internal and External Validity

The ExteNET trial is a prospective, randomized, double blind, phase III trial. As originally conceived, the trial was well-designed; however, multiple amendments to the trial protocol relating to changes in trial Sponsor led to problems with the trial particularly relating to follow up of the ITT population. The CGP raised several concerns in interpreting the ExteNET trial data, which are summarized below:

- There were 13 Amendments to the trial protocol related to changes in sponsorship by three companies, the most significant of which were amendments 3, 9 and 13. Amendment 3 restricted recruitment to higher-risk patients, defined as those with node-positive disease who had completed adjuvant trastuzumab up to one year previously. Amendment 9 stopped enrollment after 2840 patients had been randomly assigned and shortened survival follow-up from 5 to 2 years. Amendment 13 restored the primary endpoint of IDFS at 2 years in an ITT population, 1420 in each group, and in consenting patients reinstituted follow up to 5 years after randomization for disease events and deaths. However, this led to a 25% loss from the ITT population with 4.3% fewer patients available for the 5-year IDFS survival analysis in the neratinib group compared with placebo, 1028 (72.4%) versus 1089 (76.7%). The biggest threat to the internal validity of the trial, given the small number of events, is the high percentage of patients lost to follow-up. In order for the trial to have validity, it would need to be assumed that the rationale for being lost to follow-up at five years was not informed by disease recurrence – i.e. that the patients who were lost to follow-up had the same rates of recurrence as those not lost, and if there was a difference that it was not higher in the intervention group. The sponsor indicated 5-year analyses were performed in the ITT population in order to minimize selection bias resulting from excluding non-reconsented patients.
- The data supporting the funding request is not from a pre-specified subgroup analysis, but rather a post-hoc exploratory analysis that was neither powered nor controlled for multiplicity, so these results should be considered hypothesis generating and interpreted with caution. In looking at subgroups of patients who may or may not benefit from treatment with neratinib, none of the pre-specified subgroups assessed in the trial had a significantly different relative benefit from neratinib on interaction testing. HR-positive patients had a better appearing hazard ratio (0.60) and an absolute reduction in risk of invasive recurrence or death of 4%, compared to a hazard ratio of 0.95 and no apparent risk reduction in HR-negative patients. Although biologic plausibility exists for this outcome – particularly given how HR-negative recurrences may have already happened prior to the time of randomization in this study - the interaction test results suggest that we should not over-interpret this finding and the biologic rational for neratinib working preferentially in a subset of HR positive, HER2-positive breast cancer remains largely unexplained. Therefore, the sponsor's assumption that the patient subgroup with the better hazard ratio is 'true' is a potential source of bias. The CGP acknowledge the uncertainty of using this result to select a specific population for drug registration and reimbursement.
- Approximately one quarter of trial patients received neoadjuvant therapy and had to have residual disease after surgery. There is increasing use of neoadjuvant therapy as part of standard care, with strong evidence of a better prognosis in those with a pCR at surgery; therefore, the CGP felt it is unlikely that such patients would benefit from extended adjuvant neratinib therapy. Similarly, if other anti-HER2 drugs such as pertuzumab and/or T-DM1 are incorporated into neoadjuvant regimens, it is difficult to extrapolate the small benefits of extended neratinib therapy shown in the ExteNET trial to this setting.
- Over the duration for the ExteNET trial, several significant studies of anti-HER2 agents used in the (neo)adjuvant setting have been in progress, and in some cases, results have been reported. The latter include adjuvant pertuzumab in combination with trastuzumab (APHINITY)[9] and adjuvant T-DM1 in patients with residual disease after neoadjuvant therapy (KATHERINE).[10] Although these agents

are not yet widely available for adjuvant therapy in Canada, it is likely the changing treatment landscape will influence decisions about whether neratinib is likely to provide additional benefit, and thus uptake of the drug. Input from the registered clinician group of CCO suggests that the improved outcome (IDFS) reported for patients receiving T-DM1 in the KATHERINE trial will be practice-changing and may supersede neratinib in the neoadjuvant setting.

- Although extended neratinib therapy does align with an important patient value, expressing the need for additional effective treatments to reduce recurrence, low toxicity and maintained HRQoL were also thought to be important, and currently the balance of the risk/benefit ratio is unclear.
- As far as the validity of endpoints is concerned, the outcome of IDFS has a moderate to strong level of surrogacy for meaningful outcomes such as OS in early stage HER2-positive breast cancer.[11] This surrogacy is threatened if a large number of events are ipsilateral or contralateral recurrence, if treatment for metastatic disease is extremely effective/curative, or if there is a significant competing risk of death. Neither of these conditions exist with this cancer and patient population. The surrogacy of IDFS for OS is also threatened at a low event rate, which is true in this trial, so the certainty that this regimen will provide a benefit in terms of OS is moderate at best.[14]

Following the posting of the pERC initial recommendation, the CGP reviewed and discussed the feedback received from the stakeholder groups who stated they disagreed with pERC's initial recommendation to not reimburse neratinib as extended adjuvant treatment (Sponsor and Patient Advocacy Groups). To address the issues raised, the CGP provided the following comments:

- Perceived misinterpretation of subgroup analysis results -in response to feedback that the subgroup analysis results from the trial were misinterpreted, the CGP and pCODR Methods Team want to highlight that while HR status and time from completion of trastuzumab were individually pre-specified as subgroups of interest in the trial protocol the subset of patients from these subgroups that was used to define the reimbursement patient population, patients who were HR-positive and completed trastuzumab within the previous year, was not pre-specified and was performed as a post-hoc analysis. In general, pre-specified or not, subgroup analyses are not powered to test for differences in treatment effect among categories of patient subgroups and therefore should be considered exploratory and hypothesis generating requiring confirmation in future clinical studies. In the ExteNET trial, the subgroup analysis results were not adjusted to account for multiple testing (type-1 error), and therefore, the chance of a false positive result cannot be discounted. The risk of type-1 error increases as the number of tests performed increases; and in the ExteNET trial, numerous analyses (secondary, subgroup, and sensitivity) were performed.
- Suggestion that treatments in the neoadjuvant setting minimize the clinical value of neratinib – in response to feedback that it is inaccurate to assume T-DM1 given in the neoadjuvant setting will obviate the need for extended adjuvant therapy with neratinib since many patients receive trastuzumab-based adjuvant therapy, the CGP believes that although some patients with HER2-positive tumours will never be candidates for neoadjuvant chemotherapy, and therefore might be suitable for extended adjuvant treatment with neratinib, there is little doubt among the CGP that the results of the KATHERINE trial evaluating T-DM1 will increase the number of patients treated in the neoadjuvant setting. In discussing

this issue, there was disagreement among the CGP on whether the clinical benefit associated with neratinib could be extrapolated to patients who have received T-DM1 or other HER2-directed therapy (i.e., pertuzumab) in the (neo)adjuvant setting. There was agreement, however, that a confirmatory trial of neratinib in these clinical circumstances is needed.

- Mischaracterization of protocol amendments – in response to feedback opposing the judgement that the multiple protocol amendments that occurred during the trial add to the uncertainty in determining the magnitude of clinical benefit with neratinib, the CGP is primarily concerned with Amendment #9 that involved the stopping of enrollment after 2840 patients were randomized and shortening the survival follow up from 5 to 2 years. Although follow up to 5 years was restored by Amendment #13, there was a 25% loss of patients from the ITT population, with 4.3% fewer patients available for IDFS analysis in the neratinib group compared to the placebo group. This is a notable discrepancy considering the low event rate in the trial and it may have impacted the trial results. Further, the multiple trial amendments highlight an overall limitation in the trial's design to not originally restrict enrollment to a high-risk group of patients with HER2-positive breast cancer most likely to benefit from extended adjuvant treatment.
- Validity of IDFS as a surrogate endpoint for decision-making – the CGP disagrees with the feedback that implies OS data are not required to confirm the IDFS benefit associated with neratinib. The CGP acknowledges that IDFS is a frequently used and accepted surrogate for OS in the adjuvant setting; however, when trials show only a nominal IDFS benefit, as is the case for neratinib, OS data should be required to confirm clinical benefit. This is especially true among HR-positive breast cancers which have more favourable outcomes and thus require longer duration of follow-up to establish treatment efficacy.

1.3 Conclusions

The CGP concluded there may be a small net clinically meaningful benefit with the addition of extended adjuvant treatment with neratinib following trastuzumab-based therapy for patients diagnosed with early-stage, HER2-positive, HR-positive breast cancer. This conclusion is based on the results of the ExteNET trial where neratinib demonstrated modest efficacy at reducing the risk of invasive disease or death in patients with HER2-positive, HR-positive breast cancer who completed one year of adjuvant trastuzumab-based therapy within the past year despite a frequent discontinuation rate due to GI toxicity. The toxicity of neratinib mostly is manageable with dose adjustments and supportive medications, and aggressive management and prophylaxis of diarrhea as in the CONTROL trial.

The ExteNET trial is a randomized, double-blinded, placebo-controlled trial which by design should limit sources of bias. However, a number of trial limitations exist that make interpretation of the trial data difficult; these include multiple amendments and the early decision to not focus the trial to a high-risk HER2-positive breast cancer population, which represents the greatest clinical need in adjuvant HER2-positive breast cancer. Instead, the submission is based on data from a post-hoc exploratory subgroup analysis of patients with HR-positive tumours who completed trastuzumab therapy in the previous year, which should not be considered as definitive evidence of clinical benefit and requires validation in future trials. The trial is also hindered by a short duration of follow-up. Data on OS have not yet been reported; results after a 10-year period will help to draw more definitive conclusions regarding the clinical benefit of neratinib.

If extended neratinib therapy is approved, given the small efficacy benefit and significant toxicity, uptake may be lower than anticipated for the requested indication. Individual discussions between clinicians and patients, perhaps assisted by the use of a validated online predictive algorithm, may focus on groups felt to be at high-risk for recurrence (residual disease after neoadjuvant chemotherapy, large burden of nodal disease at presentation) where the approximate risk reduction of 50% would lead to a higher absolute benefit. Expanded indications, as questioned by PAG (stage 1/small node negative tumours, longer than 1 year since completion of trastuzumab, locally recurrent or metastatic disease) are not recommended. However, for patients who receive shorter courses of trastuzumab, either due to intolerance or design (non-inferiority of 6 compared with 12 months of adjuvant trastuzumab in the PERSEPHONE trial) might benefit from extended neratinib, and this should be considered on a case-by-case basis. Only 19% of patients enrolled in the ExteNET trial had completed trastuzumab treatment longer than 12 months. It might be reasonable to allow an extra 3-month window for patients who recently completed adjuvant trastuzumab at the time funding of neratinib is initiated or consider exceptions for high-risk patients in this group on an individual basis. Male patients were not included in ExteNET but share many characteristics with female breast cancer patients. As trials will never recruit sufficient male patients to make definitive adjuvant treatment recommendations it would be reasonable to consider neratinib for those who otherwise fit the eligibility criteria of an approved funding indication. Finally, to address PAG's question on the appropriate sequence of treatments following progression on neratinib, the CGP agreed that patients with a recurrence would receive standard of care treatment for metastatic disease.

The external validity of the ExteNET trial is questionable given the evolving landscape of HER2-targeted treatment. Based on the KATHERINE trial it is expected that neoadjuvant treatment of known HER2-positive disease will be the preferred option (if feasible, particularly for higher stage disease, large tumours, and node positive disease), with T-DM1 used in patients who have residual invasive disease, and trastuzumab alone in patients who have a pCR. The CGP agreed that patients with a pCR would not benefit from neratinib in the extended adjuvant setting but disagreed whether it was fair to extrapolate neratinib to the extended adjuvant setting when T-DM1 is used.

In summary, the CGP concludes there may be a small net clinically meaningful benefit with the addition of adjuvant neratinib following trastuzumab-based therapy for patients diagnosed with early-stage, HER2-positive, HR-positive breast cancer. In these patients, the CGP believes neratinib should be started within 1 year of the completion of adjuvant trastuzumab. The CGP does not recommend the use of neratinib in patients presenting with low risk, small (<2cm), node-negative, HR-positive, HER2-positive breast cancers. The CGP acknowledges caution will be needed in extrapolating the ExteNET trial data to patients treated with adjuvant pertuzumab or T-DM1 and further study of these situations is warranted.

2 BACKGROUND CLINICAL INFORMATION

2.1 Description of the Condition

Approximately 26,900 new cases of breast cancer and 5000 deaths from breast cancer occur each year in Canadian women, making it the most common invasive cancer diagnosed in women, and the second leading cause of cancer death.[15] Of these new cases of cancer, approximately 95% are diagnosed at an early stage, prior to clinically evident metastatic disease. Unfortunately, the majority of breast cancer deaths (75-80%) occur in patients initially diagnosed with non-metastatic disease, who subsequently develop metastases. For early stage breast cancers, approximately 15% are HER2-positive, as determined by either immunohistochemistry or in-situ hybridization techniques.

HER2 is a receptor molecule important for normal breast, cardiac, and brain development, but is typically not highly expressed in adult breasts. In certain cancers, HER2 can become over-expressed on the cancer cell surface, leading to a more aggressive cancer cell that has a greater degree of metastatic potential, and death, than when it is not expressed, through activation of intracellular pathways. HER2 typically becomes over-expressed through gene amplification, and definitions of HER2 positivity depend on either showing strong presence of the HER2 receptor through immunohistochemistry staining or showing gene amplification at the DNA level. This aggressive form of breast cancer was identified as a unique subset at the end of the 20th century.

2.2 Accepted Clinical Practice

For early stage HER2-positive breast cancer, administration of trastuzumab (Herceptin, Roche), an anti-HER2 monoclonal antibody, in combination with adjuvant or neoadjuvant chemotherapy, has significantly reduced the risk of death and disease recurrence in HER2 overexpressed breast cancer. Trastuzumab works in a variety of ways, all of which are dependent on its ability to bind to the juxta-membrane domain of the HER2 molecule. Trastuzumab acts in part by HER2 pathway-dependent mechanisms - reducing HER2 signalling directly through inhibition of cleavage, dimerization, and receptor destruction, as well as by HER2 pathway independent mechanisms, such as antibody-dependent cell-mediated cytotoxicity. In 1998, trastuzumab was approved in the US for metastatic HER2-positive disease treatment and was subsequently approved by Health Canada. In 2004, several clinical trials were reported, giving trastuzumab after or with chemotherapy for the duration of one year, which showed a significant benefit in terms of overall- and disease-free survival (DFS). This led to the use of trastuzumab in the adjuvant setting which has become standard of care. In addition, several studies of neoadjuvant followed by adjuvant trastuzumab were completed and led to use of trastuzumab in the pre-operative setting.

The standard of care has remained relatively stable since 2005, with trastuzumab given for one year in total, concurrent or following adjuvant chemotherapy. Trastuzumab has been given to patients with smaller tumours over time, with the recognition that even tumours less than one centimetre have a risk of recurrence that warrants trastuzumab therapy. Changes in chemotherapy backbones have occurred, with non-anthracycline options becoming available (weekly paclitaxel, docetaxel/carboplatin etc.), but the overall base of the treatment is unchanged. Over the past several years, trials of shorter and longer durations of trastuzumab have been reported, but one year remains standard of care. In this context, the recently reported PERSEPHONE trial[16] was an open-label, randomized non-inferiority trial comparing 6 months of adjuvant trastuzumab with the standard 12 months treatment. At 5.4 years (interquartile range, 3.6-6.7) median follow up, a DFS event occurred in 265 (13%) of 2043 women in the 6-month group and 247 (12%) of 2045 women in

the 12-month group. The 4-year DFS rates were 89.4% versus 89.8%, respectively (hazard ratio=1.07; non-inferiority p=0.011). AEs and cardiotoxicity (3% versus 8%, p<0.0001) were less frequent in the 6-month arm. It remains to be seen what impact this will have on Canadian clinical practice, but it is possible that patients with lower risk HER2–positive tumours will receive abbreviated trastuzumab therapy.

Trastuzumab is generally well tolerated, but may be associated with cardiotoxicity, which although typically asymptomatic can present with congestive heart failure. This cardiotoxicity restricts adjuvant trastuzumab treatment to patients with a preserved ejection fraction of greater than 50%, and often requires dose delays, cardiology consultation, and at times stopping the trastuzumab.

Patients who receive adjuvant trastuzumab have a low rate of disease recurrence but are followed clinically after completion of therapy to assess for recurrence. If patients have HR-positive tumours, then they may receive additional medications such as tamoxifen or aromatase inhibitors. Patients may also receive adjuvant radiation therapy if they are at sufficient risk, and may or may not receive adjuvant ovarian ablation, and adjuvant bisphosphonates. If there is metastatic recurrence, patients are treated with either a restart of trastuzumab with chemotherapy and pertuzumab, or T-DM1 therapy, and although treatment may be successful at prolonging life and preserving quality of life for several years, it is not a curative situation.

Two other recent important trials of HER2-directed therapies may impact on Canadian clinical practice in early breast cancer. The APHINITY trial[9] evaluated the addition of pertuzumab versus placebo to standard adjuvant trastuzumab and chemotherapy in women with node-positive or high-risk node-negative HER2-positive operable breast cancer. Disease recurrence occurred in 71/2400 (7.1%) patients in the pertuzumab group and 210/2405 (8.7%) on placebo. Estimated 3-year IDFS rates were 94.1% versus 93.2%, respectively. A statistically significant benefit was only seen in the node-positive group, with 3-year IDFS rates of 92.0% versus 90.2% (hazard ratio= 0.77; p=0.02). The combination of pertuzumab plus trastuzumab for adjuvant therapy of HER2-positive breast cancer was evaluated by pCODR and the final recommendation (29 November 2018) was not to provide reimbursement for this therapy. Thus, adjuvant pertuzumab is not funded in most Canadian provinces.

The recently reported KATHERINE trial[10] does have the potential to change practice in the neoadjuvant setting. T-DM1 is an antibody-drug conjugate of trastuzumab and the cytotoxic agent, emtansine, a micro-tubule inhibitor. Patients with HER2-positive early breast cancer, who were found to have residual invasive disease in the breast or axilla at surgery after neoadjuvant therapy containing a taxane (with or without anthracycline) and trastuzumab, were randomized to receive adjuvant T-DM1 or trastuzumab for 14 cycles. At a pre-specified interim analysis, invasive disease or death had occurred in 91/743 (12.2%) of women receiving T-DM1 and 165/743 (22.2%) receiving trastuzumab. The estimated 3-year IDFS was 88.3% versus 77.0%, respectively (hazard ratio=0.50; p<0.001). The Data Safety Monitoring Committee recommended full analysis and disclosure of the trial results. Adjuvant T-DM1 is currently under evaluation by pCODR and access to this therapy in Canada is currently limited.

2.3 Evidence-Based Considerations for a Funding Population

The evidence-based population suitable for consideration of neratinib following completion of one year of trastuzumab therapy is patients with HER2-positive, HR-positive breast cancer, stage II or III (AJCC 7th edition), who have completed trastuzumab therapy within the previous year.

This population includes:

1. Histologically confirmed, completely excised invasive breast cancer with HER2 overexpression or HER2 amplification (approximately 15-20% of all early stage breast cancers).
2. HR-positive (approximately 50% of cases).
3. Stage II or III disease at initial treatment, or with residual node positive disease after neoadjuvant therapy (approximately 70% of HER2-positive cases).
4. No evidence of metastatic disease on clinical restaging at the completion of adjuvant trastuzumab (approximately 95% of cases)
5. Ejection fraction within normal limits at the completion of trastuzumab (approximately 85% of cases).

The total number of patients per year who would potentially be eligible for neratinib (~ 25000 X .15 X .7 X .95 X .85 X 0.5) equals approximately 1100 patients per year.

If it is assumed that approximately 50% of these patients will receive neoadjuvant therapy and risk stratified adjuvant therapy, then the number may decrease somewhat. Given the likelihood that this therapy would be used in a particularly high-risk subset of these patients (stage III disease, or residual N2 or higher disease), the number would likely be closer to 300 per year.

2.4 Other Patient Populations in Whom the Drug May Be Used

There will be a question about whether to extrapolate the results of the ExteNET trial to a second year of therapy for patients treated with adjuvant T-DM1, which may become standard over the next year for HER2-positive patients with residual disease after neoadjuvant therapy. T-DM1 works via a different mechanism than neratinib, although both are targeted predominantly at the HER2 molecule. There is evidence in the metastatic setting however that neratinib can be effective and tolerated after two lines of HER2 directed therapy, raising the possibility that there could be some benefit in an adjuvant population.

There will also be patients who do not tolerate the chemotherapy effects of T-DM1, changing to trastuzumab alone who would presumably be eligible for neratinib if at sufficient underlying risk.

Patients who stop trastuzumab prior to one year, for various reasons other than cardiac events (i.e., allergic events), may still benefit from neratinib, again if the underlying risk is significant enough. Patients who receive only six months of trastuzumab therapy (as in the PERSEPHONE trial) will typically be those at a low underlying risk of relapse, so likely will not receive adjuvant neratinib.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups provided input on neratinib (Nerlynx) for HER2-positive breast cancer in patients who completed adjuvant trastuzumab (Herceptin)-based therapy within the past 12 months: Canadian Breast Cancer Network (CBCN) and the Canadian Organization for Rare Disorders (CORD).

CBCN submitted information obtained from two surveys: the 2017 Breast Cancer Patient Survey and the 2019 Breast Cancer Treatment Experience Survey, the latter of which was in collaboration with CORD. The 2017 survey was distributed online to Canadian patients from June to October 2017 who experienced a breast cancer diagnosis. Patients were contacted through CBCN's communication channels including social media and newsletters. There were 278 survey respondents; all were female and 27 had HR- and HER2-positive early stage breast cancer. The ages of the 27 respondents were: 30-39 years (n = 2); 40-49 years (n = 6); 50-59 years (n = 5); 60-69 years (n = 2); 70-79 years (n = 1); the remaining 11 respondents did not indicate their age. None of the respondents indicated they had experience with neratinib.

The 2019 Breast Cancer Treatment Experience Survey was developed jointly by CORD and CBCN. It was distributed online by CBCN through their database between April 15-29, 2019. Of 65 survey respondents, CBCN considered the 24 respondents who had HER2-positive breast cancer and were diagnosed early stage (0, I, II, III). None of the 24 respondents had experience with neratinib. CORD also considered the responses of 34 patients who identified as either HER2-positive or borderline. CORD's respondents identified their cancer stage as follows: stage I (about 15%), stage II (24%), stage III (almost 30%), stage IV (21%);12% of respondents reported staging was unknown or unsure. Time since diagnosis in years was largely >5 (35%), 1-2 (29%), or 2-5 (29%). Only two respondents (6%) had been diagnosed for less than 12 months. The grading of cancer was as follows: grade 1 (9%), grade 2 (26%), grade 3 (50%), unsure or no grade (15%). Age of diagnosis was mostly between 35-55 (53%) or 55-65 years (nearly 30%). Fewer respondents were diagnosed over 65 (12%) or under 35 years (6%). Two respondents indicated that they had experience with neratinib.

CORD also conducted patient interviews. Phone interviews were conducted by CORD between March-April 2019 with five female breast cancer patients living in Canada who had been treated with neratinib. The patients were recruited through clinicians who had participated in clinical trials, extended trials, or had prescribed neratinib through special access. All five patients were diagnosed as HER2-positive, although one patient had originally been misdiagnosed as HER2-negative. Of the CORD interviewees, patients had been diagnosed at the following stages: stage II (n=2), stage III (n=3). CORD notes that one of the stage III patients was likely stage IV by the time neratinib was received. Two of the five patients had recurrence or metastasis. Patients were aged 38-47 years at time of diagnosis and were still living between 2-8 years post-diagnosis.

No caregivers participated in either survey.

Key concerns for patients with breast cancer who participated in the CORD and CBCN surveys are the risk of recurrence and death. Current available treatments include surgery, chemotherapy, radiation, hormonal therapy, endocrine therapy and adjuvant therapy. Patients value reduced risk of recurrence, quality of life, and minimal side effects when choosing a treatment.

Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Breast Cancer

CBCN described the significant impact a diagnosis of early-stage HER2-positive breast cancer has on the physical and emotional wellbeing of patients. CORD also emphasized the

negative emotional impact of a breast cancer diagnosis and treatment. No information was provided about specific side effects associated with the cancer. Most early stage breast cancer patients will undergo a variety of treatments (surgery, chemotherapy, hormone therapy, targeted therapy, radiation) that disrupt their daily lives, and many come with side effects. CBCN noted that patients are mindful of the risks of recurrence and death as HER2-positive breast cancer is associated with a more aggressive cancer. CORD adds that there are challenges associated with access to treatment in terms of finances, travel, and social support.

3.1.2 Patients' Experiences with Current Therapy for Breast Cancer

CORD interviewees (n=5) and survey respondents (n=34) received the following therapies, respectively: surgery (100%, 94%), chemotherapy (100%, 90%), radiation (80% of both), hormonal therapy (40%, 53%), and endocrine therapy (60%, 57%). They also received trastuzumab (100%, 80%), and pertuzumab (none, 20%) as adjuvant therapies. It was not clear why some patients had not received trastuzumab, but it may be because they are still undergoing other forms of therapy.

Similar to CORD, the majority of CBCN's 2019 cohort of survey respondents (n = 24) had been treated with trastuzumab (67%). Respondents were also treated with surgery (88%), radiation (75%), chemotherapy with taxanes (75%), endocrine therapy (50%), hormone therapy (46%), and trastuzumab emtansine (4%). Unlike the CORD survey respondents, none of the CBCN respondents had been treated with pertuzumab.

CBCN respondents described current therapies as effective overall and reported side effects that included cardiac toxicity, fever, fatigue, diarrhea, muscle and joint pain, and nausea. Tolerability of side effects varied by individual; some described the side effects as manageable, while others found the effects challenging or were left with lasting effects (neuropathy). CBCN noted that patients find many side effects tolerable if the drug can reduce the risk of recurrence, though what is acceptable and tolerable is different for each individual.

When asked their opinion on the efficacy of available treatments for breast cancer, CORD patients reported overall that current therapies (monotherapy or combination) were effective or highly effective. The definition of effective was open to interpretation by patients. All respondents were either in remission or still undergoing treatment. Most respondents felt current therapies were manageable and/or tolerable.

CORD interviewees felt that quality of life was impacted by current therapies; interviewees cited impacts including fatigue and an inability to work, and some found it inconvenient to access treatment. CBCN also highlighted the financial burden patients experience because of breast cancer treatment.

3.1.3 Impact of Breast Cancer and Current Therapy on Caregivers

No information from caregivers was collected from either survey.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Neratinib

In CBCN's 2017 survey, over 90% of respondents indicated that reducing the risk of recurrence and the effectiveness of treatments were the most important considerations when selecting treatments. CBCN noted that the clinical evidence that neratinib reduces the risk of recurrence aligns closely with these patient values. Quality of life was an important outcome to patients, with 58% of respondents rating it as "very important" and

28% rating it as “important”. Having minimal side effects was rated as “very important” and “important” by 32% and 39% of respondents, respectively. According to CORD, the most important outcome to all patient respondents is NED (no evidence of disease) in follow-up tests.

There were five patients interviewed and two patients surveyed by CORD who had experience with neratinib. No experiential information was collected from the surveyed patients, though CORD notes that these patients may have also participated in an interview. Four interviewees received therapy through an extended clinical trial, and one had obtained the treatment through a Special Access Program. Of the five interviewees, three were no longer taking neratinib and two were still on therapy. Two of those not on therapy had completed the course of treatment, while one had switched to another therapy due to returning lesions.

All interviewees reported experiencing side effects either immediately upon starting neratinib or up to two weeks after the first dosage. The most common side effect was diarrhea, reported as severe to very severe by four interviewees and as moderate and manageable by the fifth. Loperamide was prescribed to four patients as prophylaxis prior to starting neratinib and while on therapy; interviewees reported it reduced the severity and frequency of diarrhea but did not totally resolve incidents. Interviewees indicated that the diarrhea resolved 2-4 months into treatment. Other side effects reported included vomiting, fever, stomach aches, and headaches. Liver toxicity was also raised as a concern by two interviewees, though no patients had experienced any indication of liver toxicity based on liver enzyme tests. No information was provided about quality of life other than the challenge of managing these side effects.

CBCN noted that this therapy benefits a specific and small subset of the breast cancer patient population who are at a higher risk of recurrence. The CORD interviewees explained that they chose neratinib, despite its side effects, to reduce as much as possible their chances of a recurrence or metastasis. They liked that neratinib was an oral therapy and most interviewees experienced no problems with the daily dose. Other benefits cited by interviewees were that neratinib treatment did not require continuous testing and there was a limited period of use (1 year).

3.3 Additional Information

None provided.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The PAG includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) and **a federal drug plan** participating in pCODR. PAG identified the following as factors that could impact the implementation of neratinib for early breast cancer:

Clinical factors:

- Clarity on eligible patient population
- Appropriate timeframe from completion of adjuvant trastuzumab-based therapy

Economic factors:

- Large pill burden of six tablets per day for a year
- Additional healthcare resources for monitoring and management of adverse events

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that for HR-positive, HER2-positive breast cancer who have completed adjuvant trastuzumab-based therapy within the past 12 months, patients are followed for monitoring in most jurisdictions. The ExteNET trial compared neratinib to placebo, this a relevant comparator.

4.2 Eligible Patient Population

PAG is seeking clarity on patients who would be eligible for treatment, if neratinib is recommended for reimbursement, whether the specific trial inclusion and exclusion criteria would be applied or the broader funding criteria. PAG identified that it would also be important to have clarity on patient eligibility in the following clinical settings:

- Node-negative disease
- Small tumours less than 1 cm
- Patients who are intolerant and unable to complete adjuvant trastuzumab
- Patients who completed trastuzumab therapy greater than 1 year previously
- Patients who received pertuzumab plus trastuzumab in the adjuvant and neoadjuvant settings
- Stage I HER2-positive breast cancer that received adjuvant trastuzumab

There is a potential for indication creep to stage I disease, metastatic setting, and beyond the treatment window for completion of adjuvant trastuzumab therapy.

In the ExteNET trial, patients were included if they were disease-free up to 2 years after completion of trastuzumab, this was later amended to up to 1 year previously. PAG is seeking guidance on the appropriate timeframe for treatment with neratinib from completion of one year of adjuvant trastuzumab therapy for patients currently being monitored. PAG noted patients who have completed trastuzumab adjuvant therapy within the past 2 years, may need to be addressed on a time-limited need.

PAG noted use of neratinib in the neoadjuvant or adjuvant setting without prior trastuzumab therapy is out of scope of the current review.

4.3 Implementation Factors

Neratinib is recommended at 240 mg orally (6 x 40 mg tablets) once daily for a year. PAG noted there is large pill burden with six tablets per day per year, this may be difficult for patients especially for those taking other oral medications. This may also have an impact on treatment adherence which would be a barrier to implementation.

PAG noted that one tablet strength of 40 mg would allow for dose adjustments and there would be minimal drug wastage. The recommended duration of neratinib is one year, PAG noted clinicians may want to treat beyond one year of neratinib therapy. PAG is also seeking clarity on the total duration of therapy with neratinib (i.e., one-year time frame or one year of neratinib therapy), given some patients may interrupt treatment due to toxicities or take treatment breaks.

As patients are currently monitored/observed, neratinib would be an additional therapy in a large patient population. This is a barrier to implementation. Additional healthcare resources (nursing, pharmacy, and clinic visits) would be required: supportive management (e.g., antidiarrheal prophylaxis such as loperamide) and monitoring and management of adverse effects (i.e., drug interactions with CYP3A4 inhibitors, grade 3 or 4 diarrhea/nausea, and hepatotoxicity). Long-term monitoring for cardiac toxicity would also be needed.

PAG noted that neratinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the oral route of administration, in which patients could easily use in the community, as an enabler. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their Pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate place in therapy for neratinib and if neratinib is recommended for reimbursement:

- Appropriate treatments following progression on neratinib (e.g., treatment including trastuzumab, pertuzumab, and taxane) and the appropriate timeframe following completion of adjuvant neratinib therapy (e.g., minimum disease-free interval, time from last dose of neratinib adjuvant therapy)

4.5 Companion Diagnostic Testing

HER2 testing is already available.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two registered clinician inputs were provided for neratinib for patients with HR-positive, HER2-positive early breast cancer who have completed adjuvant trastuzumab-based therapy within the last 12 months. Input was provided by one single clinician from Ontario, and one joint submission on behalf of three oncologists from Cancer Care Ontario (CCO). A summary of their input is provided below.

All clinicians identified the lack of treatments available for patients with early breast cancer and highlighted a need to improve clinical outcomes for these patients. Neratinib would not replace any current therapy, as there are no comparable extended adjuvant agents. Instead, neratinib would be an addition to the current treatment pathway for patients in this setting. Since HER2-positive disease would be confirmed prior to initial treatment with trastuzumab, no additional diagnostic testing would be required for neratinib.

Eligibility criteria from the ExteNET trial were stated to be applicable to clinical practice. Patients at high risk of relapse were suggested to benefit more from neratinib compared to low risk patients. Clinicians suggested generalizing the use of neratinib to male patients as well as female patients, as there were no clinical reasons why outcomes should differ.

There were differing opinions between the two submitted clinician inputs regarding generalizability of neratinib to other subgroup populations. The single clinician acknowledged the limited evidence and was uncertain whether to recommend neratinib for node negative patients or extend eligibility to patients who completed trastuzumab therapy within the last 2 years. The single clinician did support the use of neratinib for patients with small tumours if node positive, and for those treated with adjuvant/neoadjuvant pertuzumab or pertuzumab plus trastuzumab. The clinician also noted that patients with stage I breast cancer were included in the trial and would therefore not require expansion of the funding request. Clinicians from CCO did not recommend generalizing for any of the above eligibility criteria.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for Early Breast Cancer

Both inputs agreed that there are currently no other treatment options in the extended adjuvant treatment setting for patients with early beast cancer after adjuvant trastuzumab.

Trastuzumab emtansine is currently under review at pCODR for adjuvant treatment of patients with HER2-positive early breast cancer; both inputs highlighted the preference for trastuzumab emtansine based on the KATHERINE trial.

5.2 Eligible Patient Population

The single clinician stated that the population outlined in the funding request for neratinib aligns with patients in their clinical practice and that the inclusion criteria of the ExteNET trial can be applied to practice.

The joint clinician input commented on the generalizability of neratinib to male patients; they believed that there is no clinical reason why outcomes would differ by sex. The clinicians suggest that eligibility criteria for neratinib should not be restricted to females, and all patients with HER2-

positive, HR-positive breast cancer who have completed adjuvant trastuzumab-based therapy within the past 12 months should be eligible for neratinib.

5.3 Relevance to Clinical Practice

Both the single and the joint clinician inputs highlighted the unmet need for treatment options for patients with early breast cancer, and the need to improve clinical outcomes. The single clinician identified the treatment burden associated with neratinib and stated that as patients will have already completed chemotherapy and one year of trastuzumab, giving these patients neratinib may not be strongly recommended or accepted given the additional impact related to monitoring, toxicities and side effect management. Neratinib may be more strongly recommended for higher risk patients, including those who are node positive (especially N2) and have large tumours (T3 or T4), where a greater absolute benefit would be expected. Clinicians on behalf of CCO agreed that patients who are high risk may experience the greatest benefit from neratinib. Benefit of neratinib for low risk patients was less notable in the ExteNET trial. The absolute benefit for the overall population of early breast cancer patients is low, therefore preference would be to use neratinib for patients with a higher risk of relapse. Clinicians from CCO explained that it is difficult to supersede the results of trastuzumab alone in low-risk patients. Clinicians from CCO would prefer to use trastuzumab emtansine following neoadjuvant treatment over adjuvant trastuzumab-based therapy followed by neratinib because the results are more clinically meaningful and associated with fewer side effects.

The toxicity profile and management of adverse events associated with neratinib were stated to be similar to those for lapatinib, for which clinicians have extensive experience, as stated by the single clinician. No contraindications to neratinib were identified. As no other extended adjuvant agent currently exists, neratinib cannot be compared with any other therapy.

5.4 Sequencing and Priority of Treatments with Neratinib

Neratinib for select high-risk patients was stated to be an evidence-informed therapy by clinicians from CCO, though not a clinical priority. Neratinib may be appropriate for some patients, including patients who received surgery upfront and who did not receive neoadjuvant systemic therapy, or patients in the metastatic setting with CNS disease. The single clinician stated that neratinib would be used for patients who completed one year of adjuvant trastuzumab, as per the funding request. Neratinib would not replace any existing therapy, but it would be an additional therapy. Both the joint and individual clinician inputs agreed that neratinib is most beneficial for select high-risk patients.

5.5 Companion Diagnostic Testing

HER2-positive disease will need to be confirmed for patients to receive initial trastuzumab prior to neratinib. The necessary companion diagnostics were stated to already be funded.

5.6 Implementation Questions

5.6.1 In regards to question 5.2 above, the eligibility criteria for the ExteNET trial included a specific population compared to the broader funding request. In clinical practice, is there evidence to extend the use of adjuvant neratinib to (provided all other eligibility criteria are met):

5.6.1.1 Patients with node-negative disease?

Node negative patients were included in the trial population. The single clinician noted that while node negative patients seemed to benefit in the subset analysis, it was not further broken down by tumour size or grade, which may be important considerations. Clinicians

from CCO expressed that they would be less inclined to use neratinib for node negative patients.

5.6.1.2 Patients with stage I breast cancer that received adjuvant trastuzumab?

Differing opinions were present between the single clinician and clinicians from CCO. Clinicians on behalf of CCO responded 'no' to the question, without further detail, suggesting these patients should not receive neratinib. Conversely, the single clinician stated that stage I patients were included in the trial population and therefore an extension to the eligible population for reimbursement is not required.

5.6.1.3 Patients with small tumours less than 1 cm?

Regarding patients with small tumours (< 1 cm), patients with T1a-b tumours are expected by the single clinician to get less benefit from neratinib. However, if patients are node positive, then the single clinician suggested even patients with small tumours should have neratinib as an available treatment option. The joint clinician input stated 'no', without elaborating, in response to this question.

5.6.1.4 Patients disease-free up to 2 years after completion of trastuzumab (as the funding request is within the past 12 months)? Is there a group of patients that may have a time-limited need?

The single clinician stated that the value of using neratinib in patients who are greater than one-year post-completion of trastuzumab is unclear. The joint clinician input stated that "patients who received treatment more than 1 year following trastuzumab did not have a significant benefit".

5.6.1.5 Patients who have received pertuzumab or trastuzumab in the neoadjuvant/adjuvant therapy?

The value of neratinib among patients treated with neoadjuvant/adjuvant pertuzumab was stated to be unclear by the single clinician. However, as the benefit of pertuzumab was stated to be small and mostly in HR-negative and higher risk node positive patients, the potential overlap with respect to patient population would be minimal; the single clinician supported the use of neratinib among these patients. The clinicians on behalf of CCO did not support the use of neratinib among patients who received pertuzumab plus trastuzumab in the neoadjuvant/adjuvant setting because patients in the ExteNET trial received only adjuvant trastuzumab.

5.6.2 In regards to question 3.4 above, please consider the optimal sequencing of treatment for patients with hormone-receptor positive, ERBB2-positive breast cancer. In clinical practice, if neratinib was available,

5.6.2.1 What treatment options would be available to patients upon progression of neratinib (e.g., treatment including trastuzumab, pertuzumab, and taxane)? What would be the appropriate timeframe following completion of adjuvant neratinib therapy (e.g., minimum disease-free interval, time from last dose of neratinib adjuvant therapy)?

Clinicians on behalf of CCO indicated that patients who progress on neratinib would continue down the normal metastatic treatment paradigm and follow standard criteria. The clinicians stated that there should be no specified disease-free interval.

The single clinician stated that subsequent treatment algorithms would likely not be affected. The greatest potential overlap may be with lapatinib used with capecitabine which is used in the third or fourth line. Lapatinib combined with capecitabine might still

be of value in that setting. When patients experience progression after receiving adjuvant neratinib, the following treatment algorithm was provided by the single clinician: taxane/trastuzumab/pertuzumab (if less than one year after adjuvant trastuzumab), followed by trastuzumab emtansine, followed by lapatinib/capecitabine, followed by standard chemotherapy or clinical trials.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of neratinib as monotherapy for the extended adjuvant treatment of adult patients with early-stage HER2-positive, HR-positive breast cancer who have completed adjuvant trastuzumab-based therapy within the past year.

No relevant supplemental questions were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Reports were chosen for inclusion in the review based on the criteria in Table 3. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3: Selection criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
• Published or unpublished RCTs	• Histologically confirmed, HER2-positive early stage (I-III) breast cancer patients • Treated with adjuvant trastuzumab based therapy for at least 1 year **Subgroups of interest:** • HR status • Stage • Tumour size • Interval between trastuzumab use and neratinib initiation	• Neratinib	• Placebo • Standard treatment with no further HER2 directed therapy	**Efficacy** • OS • DFS • IDFS • Distant DFS • **Recurrence** (local and distant) • **HRQoL** **Safety** • All AEs, AEs leading to discontinuation, dose modification • AEs of interest: diarrhea, hepatotoxicity, cardiotoxicity, secondary malignancy

Abbreviations: AEs = adverse events; DFS = disease-free survival; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IDFS = invasive disease-free survival; OS = overall survival; RCTs = randomized clinical trials; HRQoL = health-related quality of life.

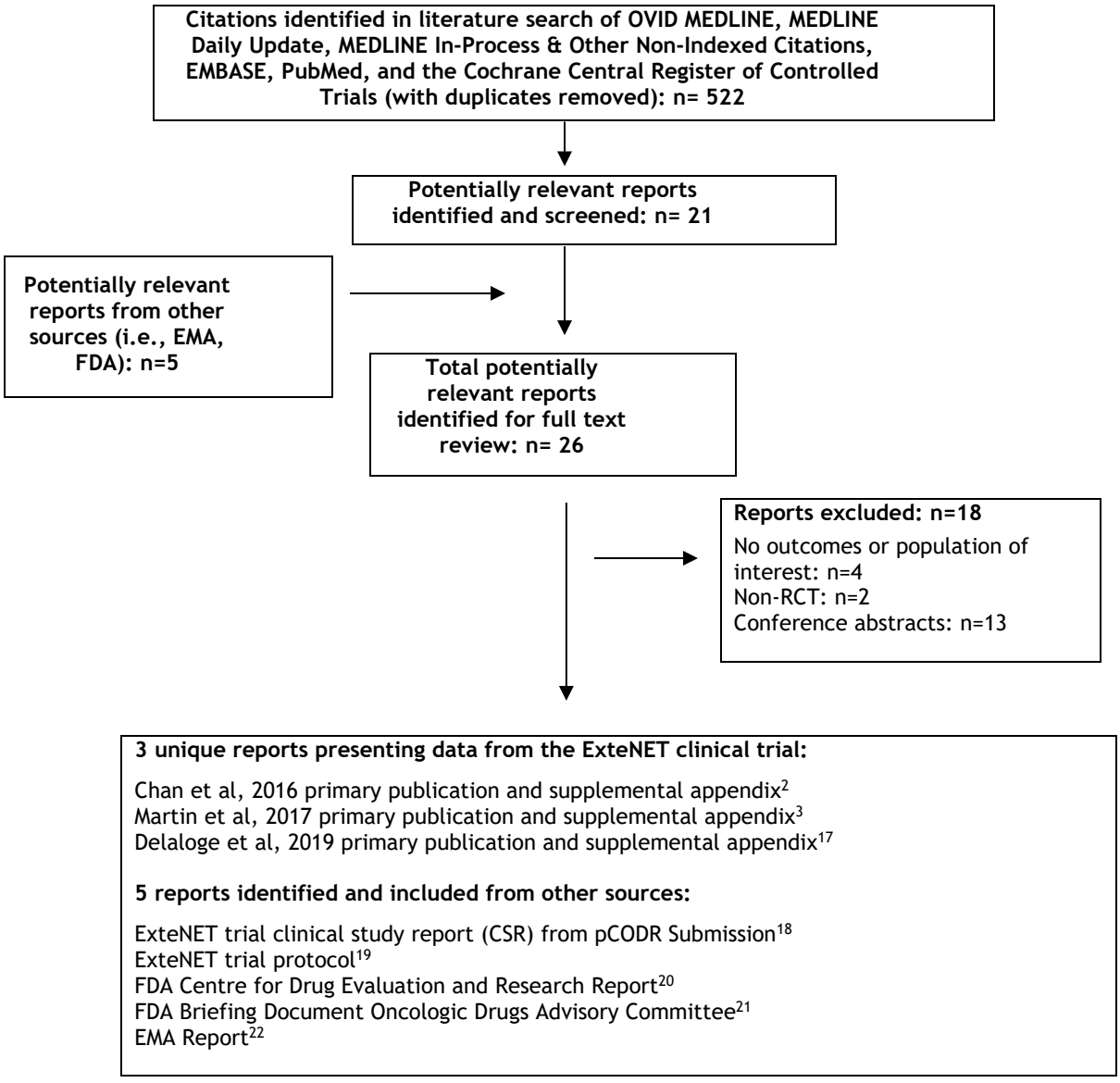
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

6.3 Results

6.3.1 Literature Search Results

Of the 466 potentially relevant reports identified, 26 were selected for full-text review. Of these, three reports were included in the pCODR systematic review [2,3,17] and 18 were excluded. Reports were excluded because they did not report outcomes or the population of interest; were not RCTs; or were early conference abstracts of published trials.

Figure 1. PRISMA Flow Diagram for Inclusion and Exclusion of Reports



6.3.2 Summary of Included Studies

The pCODR systematic review included one RCT, ExteNET (Study 3144A2-3004-WW), which assessed the efficacy and safety of 12 months of neratinib following trastuzumab-based adjuvant therapy in patients with early-stage HER2-positive breast cancer. The sponsor has requested reimbursement for a subgroup of the population in the ExteNET trial consisting of 1334 HR-positive patients who completed trastuzumab treatment within the past year.

6.3.2.1 Detailed Trial Characteristics

a) Design of the ExteNET trial

Trial and select quality characteristics of the ExteNET trial are presented in Tables 4 and 5, respectively.

Table 4: Summary of the ExteNET trial

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: ExteNET Study 3144A2-3004-WW NCT00878709[2,3] **Characteristics:** Phase III, multicenter, randomized, double-blind, placebo-controlled study **N treated:** N=2840; neratinib n=1420 and placebo n=1420 **Number of centres and number of countries:** 495 centres in Europe, Asia, Australia, New Zealand, and North and South America **Patient Enrolment Dates:** July 2009 - October 2011 **Data cut-off dates:** Primary analysis: July 2014 **Final Analysis Dates:** • 5-year follow-up completed in October 2016 • Interim data cut-off for 5-year analysis: April 2016 • Final data cut-off for 5-year analysis: March 2017 • Trial ongoing for long-term follow-up to assess OS **Funding:** Wyeth, Pfizer, Puma Biotechnology	<u>Key Inclusion Criteria:</u> • Adult patients (≥18 years of age, or ≥20 years in Japan) • Locally confirmed invasive HER2-positive breast cancer with no evidence of recurrence, and known ER/PR status • Stage 1-3 (later amended to 2-3) node-positive and node-negative (≥T1c) tumours (later amended to node-positive) • Adjuvant trastuzumab treatment completed within 2 years (later amended to 1 year) and remained disease-free; patients ≤ 1year of trastuzumab treatment must have received ≥ 8 weekly or 3 Q3W doses • ECOG PS of 0 or 1; normal organ function and a normal LVEF <u>Key Exclusion Criteria:</u> • Evidence of recurrent or metastatic disease • Clinically significant cardiac, gastrointestinal, psychiatric, or other comorbidities • Received prior neoadjuvant therapy that resulted in pCR or	Neratinib or matching placebo (1:1) 240 mg QD, taken orally Treatment given for 12 months	<u>Primary:</u> • IDFS[a] <u>Secondary:</u> • DFS-DCIS • Time-to-distant recurrence • Distant DFS • Cumulative incidence of CNS recurrences • OS • Safety <u>Exploratory:</u> • HRQoL • EQ-5D • FACT-B

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	DCIS and axillary pCR, or prior HER2 directed therapy other than trastuzumab • Patients who were unable to swallow oral medications		

Abbreviations: AE = adverse event; CNS = central nervous system; DCIS = Ductal carcinoma in situ; ECOG PS = Eastern Cooperative Oncology Group Performance Status Scale; EQ-5D = EuroQol 5-Dimensions; ER/PR = estrogen/progesterone receptor; (I)DFS = (Invasive) disease free survival; HER2 = human epidermal growth factor receptor 2; HRQoL = health related quality of life; LVEF = left ventricular ejection fraction; pCR = pathologic complete response; OS = Overall survival; Q3W = every 3 weeks.

[a] IDFS was defined as invasive ipsilateral tumour recurrence, invasive contralateral breast cancer, local or regional invasive recurrence, distant recurrence, or death from any cause.

Source: ExteNET CSR[18]

Table 5: Select quality characteristics of the ExteNET trial

Study	Treatment vs. Comparator	Primary outcome	Required / final sample size	Randomization method and allocation concealment	Blinding	ITT Analysis (Primary analysis)	Final analysis	Early termination	Ethics Approval
ExteNET Trial	Neratinib vs. Placebo	IDFS	3850[a] / 2840[b]	IVRS / IWRS	Yes	Yes	No[c]	No	Yes

Abbreviations: IDFS = Invasive disease-free survival; IV(W)RS = Interactive Voice/Web Response System

[a] Sample size originally designed to detect a hazard ratio of 0.7 for IDFS with 90% power.
[b] Two patients were allocated twice, thus 2840 patients (1420 per group) constituted the final sample size.
[c] The trial is ongoing to assess long-term outcome OS, to be done after 248 events.

Source: ExteNET CSR[18]

ExteNET is a multi-centre, placebo-controlled, double-blind, phase III RCT that assessed the comparative efficacy and safety of 12-months of treatment with neratinib versus placebo in women with early-stage HER2-overexpressed breast cancer who had received adjuvant treatment with trastuzumab. The trial was conducted at 495 centres in Europe, Asia, Australia, New Zealand, and North and South America and included 93 patients from 14 Canadian centres. There were multiple changes of sponsor control throughout the trial duration, with Wyeth being the original sponsor, which was subsequently changed to Pfizer before being transferred to Puma Biotechnology Inc. The trial consisted of three discrete parts:

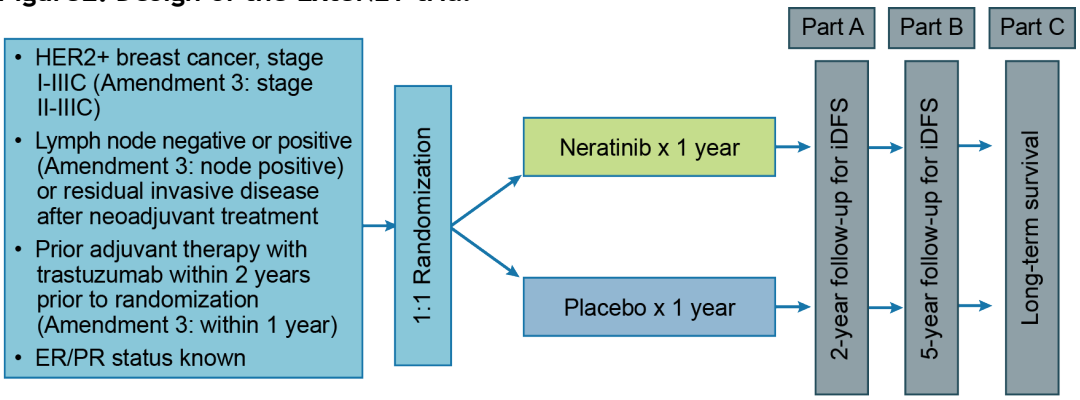
- Part A: Follow-up period of 2 years post-randomization to provide data for the primary efficacy analysis (IDFS), which was performed in July 2014.

- Part B: Extended follow-up from 3-5 years, with recurrent disease events and deaths ascertained retrospectively from medical records upon re-consent to provide data for the 5-year analysis, which was performed in March 2017.
- Part C: Long-term follow-up and analysis of OS, to be conducted after 248 deaths.

Patients were enrolled in the trial if they were at least 18 years of age; confirmed (locally and centrally) invasive HER2-positive breast cancer stages I–III (amended to only include stages II–III on Feb 25, 2010 [amendment 3]) without evidence of recurrence (based on imaging studies); completed neoadjuvant or adjuvant trastuzumab no less than 2 weeks and not more than 2 years (amended to 1 year) prior to randomization; and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients who received prior adjuvant therapy (containing an anthracycline and/or taxane, or any cyclophosphamide, methotrexate and 5-fluorouracil [CMF] type chemotherapy regimen in addition to trastuzumab) or prior neoadjuvant therapy (chemotherapy with or without neoadjuvant trastuzumab) were eligible; however, patients who received prior HER2-directed therapy other than trastuzumab, and those who achieved a pCR or DCIS and axillary pCR following neoadjuvant therapy were excluded. Further details are reported in Table 4.

Figure 2 represents the study design of the ExteNET trial. Patients were randomized using a central interactive voice and web response system to receive either neratinib or matching placebo (visually identical) in a 1:1 ratio. Randomization was generated with permuted blocks stratified by HR status (HR-positive [defined as either estrogen or progesterone receptor-positive or both] versus HR-negative [defined as estrogen and progesterone receptor-negative]), nodal status (0, 1–3, or ≥ 4), and trastuzumab adjuvant regimen (sequential versus concurrent with chemotherapy).

Figure2: Design of the ExteNET trial



Follow-up period is from time of randomization.

Abbreviations: ER/PR = estrogen/progesterone receptor; HER2 = HER2 = human epidermal growth factor receptor 2

Source : Sponsor's Clinical Summary[23]

Patients, investigators, study site personnel, and trial sponsors were blinded to treatment status until the primary analysis (in July 2014), at which time, treatment allocation was unmasked to the Puma Biotechnology team responsible for statistical analysis. Following the primary analysis, the sponsor ensured that personnel from the funding body as well as

the study team responsible for the collection of trial data remained blinded to treatment allocation using a firewall.

Protocol amendments

There was a total of 13 protocol amendments over the course of the trial, including six global amendments, three of which affected the original study design. These included changes to the eligibility criteria, sample size and study length – all initiated after recruitment had commenced.

The original protocol was issued by Wyeth in April 2009 and was designed to enrol women with invasive HER2-positive breast cancer, stages I-III, node positive or negative, tumour size ≥ 10 mm, and who completed adjuvant trastuzumab within two years of randomization. A total of 3850 patients was planned to be recruited in order to observe 337 IDFS events (the primary objective) necessary to detect a hazard ratio of 0.70 with 90% power and a one-sided significance level of 0.025. Two interim analyses were planned, at approximately 135 (for futility only) and 236 (for futility and efficacy) IDFS events. The primary analysis population was ITT. Subsequent major amendments are discussed below in brief:

- In February 2010, Pfizer, then sponsor of the trial, implemented Amendment 3. Following the change in sponsorship, recruitment was restricted to higher-risk patients, i.e. stage II-III, node-positive, who completed trastuzumab within one year of randomization. The sample size was reduced to 3300 to observe 375 IDFS events to detect a hazard ratio of 0.713 at 90% power and a one-sided 0.025 significance level. The primary analysis was to be conducted on this enriched population, referred to as the aITT population.
- In October 2011, per Amendment 9, Pfizer stopped recruitment of new patients and truncated the follow-up duration from five to two years for reasons unrelated to the trial data. This resulted in a change in the primary analysis from event-driven to time-driven. Total patient enrollment was stopped at 2850 patients. The expected sample size of the aITT population was 1700 with a total of 165 events, which would allow for a hazard ratio of 0.67 to be detected with 83% power at a one sided 0.05 significance level. Additionally, data for exploratory endpoints were no longer collected.
- In January 2014, Puma Biotechnology, the current funder of the trial, implemented Amendment 13. This amendment restored the original primary analysis, i.e. 2-year IDFS data in the ITT population (which included lower-risk patients). Additionally, patients were required to re-consent to extended follow-up for the 5-year analysis of IDFS and long-term analysis of OS. Despite the time-driven analysis, it was expected that a total of 241 events would be observed, which would allow for a hazard ratio of 0.67 to be detected with 88% power at a one sided 0.025 significance level.

Disease assessment

During the first two years (part A), patients underwent physical examinations every three months during year 1, and every four months during year 2. Mammograms were done annually and computed tomography (CT) or bone scans were done if clinically indicated. Among patients who discontinued the treatment period due to distant recurrence, information on survival and first use of anti-cancer treatment other than neratinib continued to be collected. This information was also collected for patients who completed the entire 12-month treatment period or who discontinued treatment for reasons excluding

distant recurrence. In addition, all scheduled physical exams were continued to be performed in these patients.

Subsequent to the primary analysis period, physical examination and mammogram schedules during years 3-5 (part B) were based on the local standard of care, as determined by the treating physician. Information on recurrent disease events and deaths were ascertained retrospectively from the medical records of patients who re-consented to continue the trial.

Monitoring of AEs was carried out until 28 days after the last dose of study drug and graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE), version 3.0. Thereafter, data on all treatment-emergent SAEs were collected and will continue until the final analysis (OS) is reported. Among patients who discontinued treatment, all attempts were made to continue their scheduled physical assessments and the collection of efficacy and safety data (including reasons for loss to follow-up or withdrawal of consent).

Study endpoints

The primary efficacy endpoint was IDFS at 2-years, defined as the time from randomization to the first occurrence of any one of the following: invasive ipsilateral breast tumour recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause. Notably, this definition differs from the standardised efficacy endpoints (STEEP) system in adjuvant breast cancer trials, as the criterion of second non-breast primary events was excluded from the definition used in the trial based on feedback from the US Food and Drug Administration (FDA) and European Medicines Agency's European Committee for Medicinal Products for Human Use (CHMP).

All IDFS events that had occurred up to the data cut-off date of 2 years + 28 days from randomization were included in the primary analysis, unless the events occurred after two or more missing physical exams. Patients who did not have an IDFS event by the data cut-off date had their IDFS time censored at the date of the last physical exam, either scheduled or unscheduled, occurring within 2 years, 4 months, and 28 days from randomization. Patients who had an IDFS event after two or more missing physical exams (8-month gap) had their IDFS times censored at the last available physical exam prior to the event. Following a global amendment in January 2014 (amendment 13), the efficacy endpoint was extended to a 5-year follow-up period.

The secondary efficacy endpoints assessed in the trial included the following:

- DFS including ductal carcinoma in situ (DFS-DCIS), defined as time from randomization to the first occurrence of a DFS or DCIS event
- Time-to-distant recurrence (TTDR), defined as time between randomization and the date of the first distant tumour recurrence, or death from breast cancer
- Distant disease-free survival (DDFS), defined as time from randomization to the first distant tumour recurrence or death from any cause
- CNS recurrence, defined as cumulative incidence of time from randomization to CNS recurrence as first distant recurrence, occurred either as isolated CNS metastases or concurrently with other sites of metastatic disease
- OS, defined as time from the date of randomization until the date of death, censored at the last date known alive.

Any patient who did not experience any of the above events by the data cut-off date were censored at the date of their last physical examination.

A number of exploratory endpoints were also evaluated. These included biomarker analyses (including central confirmation of HER2 status) and HRQoL measured using (i) the FACT-B version 4, for breast cancer-specific quality of life; and (ii) the EQ-5D for generic quality of life.

The FACT-B is a 37-item questionnaire with 4 subscales assessing physical, social/family, emotional, and functional well-being, with an additional breast cancer-specific subscale (9 items). Patients rate each item on a five-point scale (0 = not at all; 4 = very much), with the total FACT-B score ranging from 0 to 144. The trial used a MCID of 7-8 points for the total FACT-B score, and 2-3 points for the FACT-B subscales.[17] FACT-G, also assessed in the trial, includes a general questionnaire that consists of the first four subscales of FACT-B. An MCID of 5-6 points for total FACT-G score was used in the trial.[17]

The EQ-5D is a generic preference-based HRQoL instrument that has been applied to a wide range of health conditions and treatments. EQ-5D consists of two parts: a descriptive system consisting of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three or five possible levels (depending on whether the 3L or 5L version is chosen); the ExteNET trial used the 3L version.[17] Respondents are asked to choose one level (e.g. no, some, or extreme problems) that reflects their own health state for each of the five dimensions. Scores for each domain are then added into an index score. The second part is a vertical, calibrated 20 cm visual analog scale (EQ-VAS) that has endpoints labeled 0 and 100, with anchors of 'worst imaginable health state' and 'best imaginable health state', respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ-VAS which best represents their own health on that day. The MCID for the EQ-5D index and VAS score varies by disease; the trial used an MCID of 0.09-0.10 and 7-10 units for the index and VAS scores, respectively.[17] For both instruments, a higher score indicates a better quality of life.

Statistical Analysis

Analysis Populations: Four analysis populations were used in the trial, which are defined below. Table 6 shows the number of patients in each study population in the two treatment groups. It should be noted that results of the aITT and centrally-confirmed HER2 population will not be reported in this review.

- The ITT population, defined as all patients who were randomized into the trial. Patients were analyzed according to the treatment group they were originally assigned, irrespective of the treatment received. All primary and secondary efficacy endpoints were analyzed in this population.
- The aITT population, comprised of a higher-risk subgroup, which included patients with node-positive disease and those who were randomized within one year of trastuzumab treatment.
- The safety population was defined as all patients who received at least one dose of the study drug. Patients were analyzed according to the treatment they received, regardless of the treatment group to which they were randomized. All safety analyses were done in this population.
- The centrally-confirmed HER2-positive population, defined as all randomized patients who were centrally tested to be HER2-postive. This population was used for a sensitivity analysis of the primary efficacy endpoint.

Table 6: Study populations

	Neratinib	Placebo	Total (N=3278)
All Enrolled Patients			3278
Screen Failed			355
Randomized	1420	1420	2840
Intent-to-treat (ITT) Population[a] - n	1420	1420	2840
Amended Intent-to-treat (aITT) Population[b] - n	938	935	1873
Centrally Confirmed erbB-2 Positive Population[c] - n	741	722	1463
Safety Population[d] - n	1408	1408	2816
Other			83

[a] The ITT population includes all randomized patients with the exceptions documented in the SAP. Patients were analyzed by the randomized treatment arms regardless of the actual treatment received
[b] The aITT population includes all patients randomized under global amendment 3 or later amendment, or all patients randomized prior to implementation of global amendment 3 if they met the following key criteria: 1. All patients with node-positive disease and 2. All patients randomized within 1 year from completion of prior trastuzumab therapy
[c] The Centrally Confirmed erbB-2-Positive population includes all patients randomized who were confirmed by central testing to be erbB-2 positive
[d] The safety population includes all patients who received at least one dose of IP. Patients were analyzed by the actual treatment arms regardless of the randomized treatment
Other included 83 patients who were consented into the study but had no screen failure documented and were not randomized

Source: ExteNET CSR[18]

Sample size and power: According to the original protocol, an estimated sample size of 3850 patients was established by assuming a hazard rate of 0.056 events/year/patient in the placebo group based on a weighted average of mean hazard rates from the HERA,[24] BCIRG 006,[25] and NCCTG N9831[26] trials. Additionally, a 15% dropout rate in the first year and a 5% annual dropout rate thereafter was assumed. At this rate, it was projected to take 3.6 years to accrue the planned 337 IDFS events. Following the implementation of Amendment 3, the following assumptions were made: placebo group hazard rates of 0.079 and 0.049 events/person/year for the 1st and 2nd year, respectively; IDFS hazard ratio of 0.667, and average hazard rates for dropout of 0.0513 and 0.0160 events/person/year for the 1st and 2nd year, respectively. Based on the assumed estimates, the study was expected to accrue 241 IDFS events with approximately 88% power at a 2-sided 5% significance level. Thus, a lower than anticipated hazard rate for IDFS would lead to fewer than expected IDFS events and consequently the power of the study would be diminished. A formal power calculation was not done for the primary analysis following Amendment 9, as follow-up was truncated to two years from randomization and therefore a total number of events was not pre-specified.

Sample size and power calculations were not performed for the 5-year efficacy endpoints with the exception of OS. OS will be tested following 248 deaths, which will allow for a hazard ratio of 0.70 to be detected with 80% power at a 2-sided 5% significance level.

Interim analysis: As per the final protocol amendment, no interim analyses were conducted due to the cessation of patient recruitment. An interim analysis for OS is planned after accrual of 124 deaths (50% of 248 deaths for OS analysis).

Analysis method: All time-to-event endpoints were analyzed with log-rank tests stratified by HR status, nodal status (dichotomized ≤ 3 nodes versus ≥ 4 nodes), and trastuzumab given sequentially versus concurrently with chemotherapy. The stratified Cox proportional hazards model was used to estimate the hazard ratios and the accompanying 95% confidence intervals. The Kaplan–Meier (K-M) method was used to estimate 2-year survival rates and annual event-free survival. For CNS recurrences, a cumulative incidence with

competing risk analysis was done, and between-treatment comparison was tested using Gray's test.

HRQoL was tested between treatment groups by comparing changes in score from baseline using analysis of covariance (ANCOVA), with baseline scores as a covariate and no imputation for missing values. Safety data were generally reported descriptively. Notably, an analysis of mean grade of diarrhea over time was performed to examine the timing, severity, and duration of diarrhea.

Statistical significance and multiplicity: All statistical tests for efficacy endpoints were 1-sided at a significance level of 0.025 unless stated otherwise. In order to control for multiplicity, a hierarchy of analysis was followed whereby IDFS and OS both needed to be significant at the nominal level (1-sided level of significance of 0.025) before declaring the statistical significance of OS. An adjustment for multiplicity was not required for the secondary efficacy endpoints, since these were considered supportive evidence of IDFS only. All 5-year efficacy endpoints, with the exception of OS, were considered sensitivity analyses in the study protocol; therefore, no adjustment for multiplicity was made and results from these analyses should be considered descriptive.

Censoring: The sponsor indicated that the censoring rule was updated in the final version of the statistical analysis plan (SAP), dated April 6, 2016.[27] All information herein is as described in the final SAP. Patients who did not experience any disease recurrence up to the cut-off date of the primary analysis (2 year + 28 days post-randomization) and who did not re-consent for additional follow-up were censored at the date of their last physical examination (occurred within 2 years + 4 months + 28 days post-randomization). Patients who re-consented for longer follow-up and did not experience any IDFS events were censored at the date of their last physical examination (occurred within 5 years + 6 months post-randomization). Patients who had an event following two missed assessments (a gap of eight months during years 1 and 2, or 12 months during years 3–5) were censored at the last available physical examination prior to the event.

Subgroup and sensitivity analyses: Pre-specified subgroup analyses were conducted to examine whether the treatment effect differed based on stratification factors and other baseline characteristics; and tests for interaction were performed to assess the homogeneity of treatment effect across categories of the subgroups. Notably, the target patient subgroup that is the focus of the reimbursement request (HR-positive patients who completed trastuzumab within the previous year) was not pre-specified in the trial protocol/SAP and analyzed *post-hoc*; therefore, results of this analysis should be considered descriptive.

A number of protocol-defined sensitivity analyses were conducted in part A (years 1 and 2) of the trial to examine the robustness of the primary analysis results. In part B of the trial (years 3-5 post-randomization), analyses of IDFS data were considered sensitivity analyses, as were analyses of IDFS in the higher-risk aITT population (node-positive disease and randomized within one year of trastuzumab treatment).

A sensitivity analysis was conducted to assess the impact of early dropouts (censored < 3 months) on the primary analysis after 127 patients in the neratinib group and 44 patients in the placebo group dropped out within three months of treatment for reasons other than recurrent disease. Briefly, early dropouts in the neratinib group were assumed to have IDFS events following the rate observed in the placebo group. IDFS events for the neratinib early dropout patients were imputed via resampling (10,000 times) from the placebo patients matched by the stratification factors.

b) Populations

Between July 2009 and October 2011, 3278 patients were enrolled to participate in the trial, of which 2840 were randomized and constituted the ITT population. At the end of the 2-year primary analysis period, 2117 patients re-consented to an extended follow-up for 5 years. Baseline characteristics of both study populations are presented in Table 7.

Overall, there were no notable imbalances between the treatment groups with respect to demographic and clinical characteristics and treatment history in either period of the trial. The ITT population was comprised of all women with a median age of 52.3 years, and 59.9% were over the age of 50 years. Patients were predominantly White (81.0%), followed by Asian (13.6%); and approximately a third of the population were from sites in North America (35.1%) and Western Europe, Australia, and South Africa (35.9%). The trial included 93 patients from 14 Canadian centres.

At baseline, the median BMI in the ITT population was 26.42, 53.3% were post-menopausal, and the majority of patients (99.8%) had an ECOG performance status of 0 to 1. In terms of nodal status, 46.8% of patients had 1-3 positive nodes, 29.6% had ≥ 4 positive nodes, and 23.6% were node-negative. More than half of patients were HR-positive (57.4%) and received concurrent trastuzumab and chemotherapy prior to randomization (62.3%). In total, 71.6% of the patients had stage II-III tumours, 47.3% had poorly differentiated histology, and 94% had ductal carcinoma. Median time from diagnosis to randomization was 22.05 months.

In terms of prior anti-cancer treatment, the majority of patients received prior radiotherapy (80.3%) and chemotherapy (99.7%), 34.5% had a lumpectomy, and 65.5% had a mastectomy. All patients received prior trastuzumab; 99.7% in the adjuvant setting and 17.2% initiated trastuzumab in the neoadjuvant setting. The median time from last treatment with trastuzumab to randomization was 4.50 months and the majority of patients had trastuzumab ≤1 year from randomization (80.9%). Patients received adjuvant trastuzumab for a median of 11.43 months. Notably, a total of 721 (25.4%) patients received prior neoadjuvant therapy. Among all patients, 126 (4.4%) achieved a pCR, 556 (19.6%) had not achieved a pCR, and for 39 (1.4%) patients, the pCR status was unknown. Approximately 94.8% HR-positive patients and 3.2% HR-negative patients had prior endocrine therapy with anti-estrogen and aromatase inhibitors as the most frequent endocrine therapy.

Patients who re-consented for part B of the trial had largely a similar distribution of demographic and clinical characteristics compared to the ITT patient population and treatment groups were well-balanced in all characteristics. Additionally, this pattern was consistent in the target patient subgroup of interest for this review (patients with HR-positive and completed trastuzumab within the past year), with no notable differences between the treatment groups (Table 8).

Table 7: Baseline characteristics of patients in the ExteNET trial

	Intention-to-treat population (n=2840)		Re-consented patients (n=2117)	
	Neratinib (n=1420)	Placebo (n=1420)	Neratinib (n=1028)	Placebo (n=1089)
Age (years)	52 (45–59)	52 (45–60)	52 (45–59)	53 (45–60)
Region				
North America	519 (37%)	477 (34%)	326 (32%)	320 (29%)
Western Europe, Australia, New Zealand, and South Africa	487 (34%)	532 (37%)	369 (36%)	432 (40%)
Asia Pacific, eastern Europe, and South America	414 (29%)	411 (29%)	333 (32%)	337 (31%)
Menopausal status at diagnosis				
Premenopausal	663 (47%)	664 (47%)	486 (47%)	506 (46%)
Postmenopausal	757 (53%)	756 (53%)	542 (53%)	583 (54%)
Nodal status*				
Negative	335 (24%)	336 (24%)	216 (21%)	261 (24%)
1–3 positive nodes	664 (47%)	664 (47%)	506 (49%)	510 (47%)
≥4 positive nodes	421 (30%)	420 (30%)	306 (30%)	318 (29%)
Hormone receptor status*				
Positive (ER positive, PR positive, or both)	816 (57%)	815 (57%)	603 (59%)	615 (56%)
Negative (ER and PR negative)	604 (43%)	605 (43%)	425 (41%)	474 (44%)
Previous trastuzumab regimen*				
Concurrent	884 (62%)	886 (62%)	621 (60%)	671 (62%)
Sequential	536 (38%)	534 (38%)	407 (40%)	418 (38%)
T stage				
T1	440 (31%)	459 (32%)	315 (31%)	359 (33%)
T2	585 (41%)	555 (39%)	431 (42%)	421 (39%)
≥T3	144 (10%)	117 (8%)	104 (10%)	89 (8%)
Unknown	250 (18%)	288 (20%)	178 (17%)	220 (20%)
Missing	1 (<1%)	1 (<1%)	..	..
Histological grade of tumour				
Undifferentiated or poorly differentiated	670 (47%)	689 (49%)	495 (48%)	538 (49%)
Moderately differentiated	461 (32%)	416 (29%)	331 (32%)	311 (29%)
Well differentiated	76 (5%)	65 (5%)	57 (6%)	50 (5%)
Unknown	213 (15%)	241 (17%)	145 (14%)	190 (17%)
Previous surgery	..	..	..	..
Lumpectomy only	468 (33%)	511 (36%)	343 (33%)	392 (36%)
Mastectomy	951 (67%)	908 (64%)	684 (67%)	696 (64%)
Missing	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Previous radiotherapy				
Yes	1130 (80%)	1150 (81%)	830 (81%)	875 (80%)
No	290 (20%)	270 (19%)	198 (20%)	214 (20%)
Previous neoadjuvant or adjuvant therapy†				
Yes	1420 (100%)	1420 (100%)	1028 (100%)	1089 (100%)
Trastuzumab	1420 (100%)	1420 (100%)	1028 (100%)	1089 (100%)
Anthracycline only	136 (10%)	135 (10%)	102 (10%)	109 (10%)
Anthracycline plus taxane	962 (68%)	965 (68%)	725 (71%)	762 (70%)
Taxane only	318 (22%)	316 (22%)	198 (19%)	216 (20%)
Non-anthracycline or taxane	4 (<1%)	4 (<1%)	3 (<1%)	2 (<1%)

(Table 1 continues on next page)

	Intention-to-treat population (n=2840)		Re-consented patients (n=2117)	
	Neratinib (n=1420)	Placebo (n=1420)	Neratinib (n=1028)	Placebo (n=1089)
(Continued from previous page)				
Duration of previous adjuvant trastuzumab therapy (months)	11·5 (10·9–11·9); n=1413	11·4 (10·8–11·9); n=1416	11·5 (10·9–11·9); n=1023	11·4 (10·8–11·9); n=1086
Time from last dose of trastuzumab to randomisation (months)	4·4 (1·6–10·4)	4·6 (1·5–10·8)	4·5 (1·7–10·4)	4·3 (1·5–10·7)
Concomitant endocrine therapy for hormone receptor-positive tumours‡				
No	56 (7%)	51 (6%)	33 (6%)	28 (5%)
Yes	760 (93%)	764 (94%)	570 (95%)	587 (95%)
Anti-oestrogen only	375 (46%)	347 (43%)	294 (49%)	281 (46%)
Anti-oestrogen and aromatase inhibitor (sequential)	20 (3%)	34 (4%)	31 (5%)	31 (5%)
Aromatase inhibitor only	362 (44%)	379 (47%)	242 (40%)	272 (44%)
Neither anti-oestrogen nor aromatase inhibitor	3 (<1%)	4 (<1%)	3 (<1%)	3 (<1%)

Data are n (%) or median (IQR), unless otherwise specified. Because of rounding, not all percentages add up to 100. ER=oestrogen receptor. PR=progesterone receptor. *Stratification factor collected from the interactive voice and web-response system. For nodal status, the number of positive nodes was taken at the time of initial diagnosis (for those who received adjuvant therapy) or surgery (for those who received neoadjuvant therapy). Patients with residual invasive disease in the breast, but node-negative or unknown nodal status in the axilla after neoadjuvant therapy, were included in the category of 1–3 positive nodes. †The proportion of patients who received neoadjuvant chemotherapy was 25% (n=247) in the neratinib group and 27% (n=282) in the placebo group. ‡Percentage is based on the number of patients with hormone receptor-positive tumours. Tumours were assessed as being ER or PR positive on the basis of local pathology laboratory cutoffs. There was no protocol specification as to whether a 1% or 10% threshold should be used.

Source: Reprinted from The Lancet Oncology, Vol.18 number 12, Martin M, Holmes FA, Ejlertsen B, et a, 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, Pages No.1688-1700, Copyright (2017), with permission from Elsevier.[3]

Table 8: Baseline characteristics of target patient subgroup and ITT population

Study population	HR-positive and ≤1 year from last dose of trastuzumab to randomization (n=1334)		HR-positive and ≤1 year from last dose of trastuzumab to randomization and with no pCR on neoadjuvant therapy (n=295)		ITT population (n=2840)	
	Neratinib (n=670)	Placebo (n=664)	Neratinib (n=131)	Placebo (n=164)	Neratinib (n=1420)	Placebo (n=1420)
Median (range) age, years	51 (25–83)	51 (23–78)	49 (25–76)	49 (26–76)	52 (25–83)	52 (23–82)
Race, n (%)						
White	564 (84)	544 (82)	98 (75)	130 (79)	1165 (82)	1135 (80)
Asian	77 (11)	88 (13)	24 (18)	26 (16)	188 (13)	197 (14)
Black	11 (2)	19 (3)	3 (2)	3 (2)	27 (2)	47 (3)
Other	18 (3)	13 (2)	6 (5)	5 (3)	40 (3)	41 (3)
Nodal status,[a] n (%)						
Negative	130 (19)	125 (19)	15 (11)	20 (12)	335 (24)	336 (24)
1–3 positive nodes	339 (51)	334 (50)	85 (65)	96 (59)	664 (47)	664 (47)
≥4 positive nodes	201 (30)	205 (31)	31 (24)	48 (29)	421 (30)	420 (30)
Hormone receptor status,[ab] n (%)						
Positive	670 (100)	664 (100)	131 (100)	164 (100)	816 (57)	815 (57)
Negative	–	–	–	–	604 (43)	605 (43)
Prior trastuzumab regimen,[a] n (%)						
Concurrent	411 (61)	415 (63)	90 (69)	111 (68)	884 (62)	886 (62)
Sequential	259 (39)	249 (38)	41 (31)	53 (32)	536 (38)	534 (38)
Median (range) time from last trastuzumab dose to	3.1 (0.2–12.0)	3.3 (0.3–12.0)	3.0 (0.4–12.0)	2.8 (0.3–11.9)	4.4 (0.2–30.9)	4.6 (0.3–40.6)

randomization, months						
Prior neoadjuvant therapy, n (%)	162 (24)	192 (29)	131 (100)	164 (100)	342 (24)	397 (27)
pCR	17 (3)	21 (3)	–	–	61 (4)	65 (5)
No pCR	131 (20)	164 (25)	131 (100)	164 (100)	258 (18)	298 (21)
Unknown	14 (2)	7 (1)	–	–	23 (2)	16 (1)

Abbreviations: pCR = pathological complete response; ITT = intention-to-treat

[a] Stratification factor
[b] HR-positive defined as estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive, and HR-negative as ER-negative and PR negative

Source: Sponsor's Clinical Summary[23]

c) Interventions

Treatment dosing schedule

Patients were randomly assigned to receive once-daily oral neratinib or placebo in a 1: 1 ratio. Both study drugs were visually identical and were self-administered preferably in the morning with food. Neratinib 240 mg (6 X 40 mg tablets) or matching placebo were administered for 12 months or until disease recurrence as determined by the site investigator, or toxicity requiring discontinuation.

Dose modifications

Dose reductions to 200 mg, 160 mg and 120 mg daily were permitted for the management of toxicity. Re-escalation to the previous dose level was permitted under certain circumstances prior to Amendment 9 (described later).

Patients in the neratinib group reported ≥ 1 dose reductions more frequently compared with the placebo group (36.9% versus 8.0%) that were primarily due to AEs (31.2% and 2.6% in the neratinib and placebo groups, respectively) (Table 9).

Table 9: Summary of Dose Reductions in Safety Population

	Neratinib (N=1408)	Placebo (N=1408)
Patients With Dose Reduction[a] - n (%)		
No Dose Reduction	889 (63.1)	1296 (92.0)
One Or More Dose Reduction	519 (36.9)	112 (8.0)
Lowest Dose Reduction Level - n (%)		
No Dose Reduction	889 (63.1)	1296 (92.0)
Reduce To 200 mg/day	258 (18.3)	61 (4.3)
Reduce To 160 mg/day	148 (10.5)	13 (0.9)
Reduce To <160 mg/day	112 (8.0)	38 (2.7)
Reduce To 180 mg/day[b]	1 (0.1)	0
Dose Reduction Reason - n (%)		
Reduced Due To AE	439 (31.2)	36 (2.6)
Non-compliance	89 (6.3)	66 (4.7)
Other[c]	253 (18.0)	30 (2.1)

[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.

Source: ExteNET CSR[18]

Concomitant Medications

The following treatments were permitted during the trial:

- Standard therapies for pre-existing medical conditions and for medical and/or surgical complications
- Adjuvant endocrine therapy for HR-positive disease
- Bisphosphonates, regardless of the indication.

Prohibited Medications

The following treatments were prohibited throughout the duration of the treatment phase of the trial:

- Any chemotherapy, radiation therapy, immunotherapy, biotherapy, or surgery for breast cancer
- Any other investigational agent
- Other medications that were cautioned against during the treatment phase, which included inducers or inhibitors of CYP3A4, grapefruit juice, and St John's Wort.

Raloxifene or other selective ER modulators were not prohibited for use in approved indications (i.e. prevention or treatment of osteoporosis or osteopenia in postmenopausal women); however, its use for breast cancer was restricted since it is not approved for the adjuvant treatment of breast cancer.

In total, 2722 (96.7%) patients took ≥ 1 concomitant medication during treatment; 1395 (99.1%) in the neratinib group and 1327 (94.2%) in the placebo group. The most frequently used concomitant medications (≥ 10% by class) included the following: anti-propulsives taken by 87.2% and 15.3% of patients in the neratinib and placebo groups, respectively; aromatase inhibitors taken by 27.6% and 29.9%, respectively; anti-estrogens used by 28.6% and 27.8%, respectively; and proton pump inhibitors taken by 17.5% and 15.5%, respectively. Anilides, benzodiazepine derivatives, calcium, HMG CoA reductase inhibitors, and vitamin D And analogues constituted the other notable concomitant medications taken by ≥ 10% of patients in either group.

As previously noted, 1631 patients in the ExteNET trial were HR-positive, of which 1524 (93.4%) received concomitant endocrine therapy. The use of all concomitant endocrine therapy was balanced between the treatment groups, 760 (93.1%) in the neratinib group and 764 (93.7%) in the placebo group (Table 10).

Table 10: Summary of concomitant endocrine therapy in the ITT population

	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)
Hormone Receptor Positive Patients	816 (57.5)	815 (57.4)	1631 (57.4)
Concomitant Endocrine Therapy Use			
Yes	760 (93.1)	764 (93.7)	1524 (93.4)
No	56 (6.9)	51 (6.3)	107 (6.6)
Concomitant Endocrine Therapy - n (%)			
Anti-estrogen & aromatase inhibitor	20 (2.6)	34 (4.5)	54 (3.5)
Anti-estrogen only	375 (49.3)	347 (45.4)	722 (47.4)
Aromatase inhibitor only	362 (47.6)	379 (49.6)	741 (48.6)
Non anti-estrogen & aromatase inhibitor	3 (0.4)	4 (0.5)	7 (0.5)
Hormone Receptor Negative Patients	604 (42.5)	605 (42.6)	1209 (42.6)
Concomitant Endocrine Therapy Use			
Yes	12 (2.0)	20 (3.3)	32 (2.6)
No	592 (98.0)	585 (96.7)	1177 (97.4)

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.

Source: ExteNET CSR[18]

Extent of Exposure

A total of 2816 patients received at least one dose of the study drug, for a median treatment duration of approximately 11 months. The median actual dose intensity was 235.4 mg/day in the neratinib group and 240.0 mg/day in the placebo group, making the median relative actual dose intensity to be 98% in the neratinib group. Over 75% of patients in the neratinib group received at least 80% of the planned 240 mg/day dose during the treatment

period. Compliance was high among trial patients, with a median degree of adherence to prescribed dosage of 100% in both arms (Table 11).

Table 11: Exposure to study drug in safety population

Exposure	Neratinib N=1408	Placebo N=1408
Duration of treatment (month)		
Mean (SD)	8.23 (4.88)	10.71 (2.85)
Median (min, max)	11.60 (0.03, 13.34)	11.83 (0.13, 13.17)
Cumulative Actual Dose (mg)		
Mean (SD)	54193.93 (34205.17)	76749.32 (20841.81)
Median (min, max)	70200 (240, 92400)	85200 (960, 95040)
Compliance (%)		
Mean (SD)	98.09 (6.52)	98.91 (3.11)
Median (min, max)	100.00 (17.82, 103.33)	100.00 (59.09, 100.56)

Abbreviations: SD = standard deviation; mg = milligram ; min = minimum ; max = maximum
Compliance = actual dose intensity/prescribed dose intensity x100%

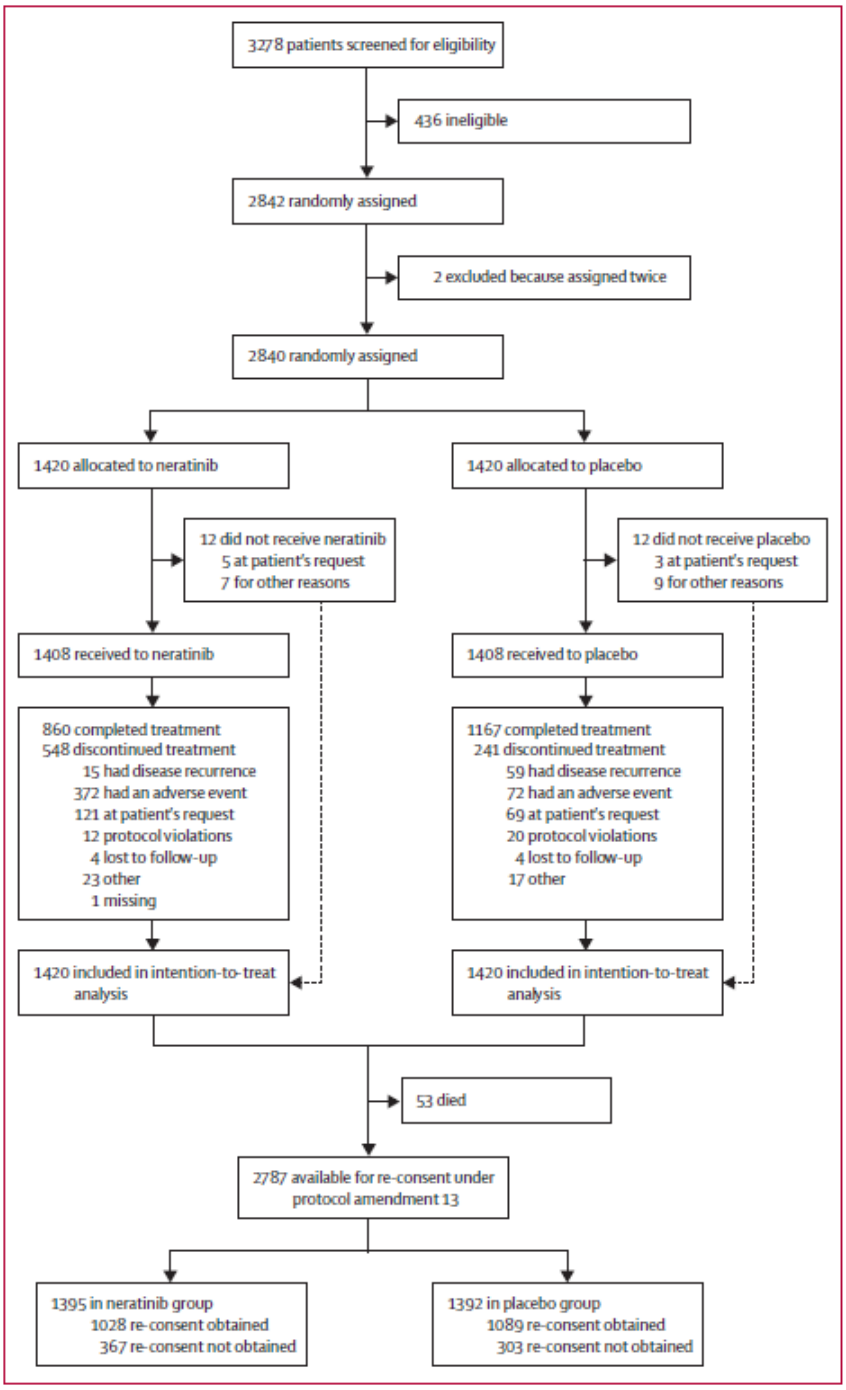
Source: Adapted from ExteNET CSR[18]

d) Patient Disposition

Figure 3 illustrates patient disposition in the ExteNET trial. Of the 3278 patients screened for eligibility, 2840 patients were randomized to receive neratinib or placebo; however, 0.8% patients in each group did not receive the study drug. Among the 2816 patients who received study drug, 72% completed the 12-month treatment phase (61.1% in the neratinib group and 82.9% in the placebo group). The higher treatment cessation observed in the neratinib group was primarily due to AEs (26.4% versus 5.1%). More patients in the neratinib group also discontinued treatment due to subject request; whereas more patients in the placebo group discontinued treatment due to disease recurrence. Additionally, less patients in the neratinib group completed part A treatment and follow-up, 77.1% versus 83.3%, primarily due to a higher subject request in this group.

A total of 1420 patients in each group were included in the ITT population for part A of the trial. At the end of the 2-year period, 53 patients died, therefore 2787 patients were available to provide re-consent for the extended follow-up of 5 years under protocol Amendment 13. Of these patients, 2117 (76%) re-consented for follow-up up to 5 years: 1028 in the neratinib group and 1089 in the placebo group. More patients in the neratinib group did not re-consent for part B of the trial compared with the placebo group, 367 versus 303, respectively.

Figure 3: Patient disposition



Source: Reprinted from The Lancet Oncology, Vol.18 number 12, Martin M, Holmes FA, Ejlertsen B, et a, 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, Pages No.1688-1700, Copyright (2017), with permission from Elsevier.[3]

Protocol Deviations

Protocol deviations in the ExteNET trial resulted from the following:

- Inclusion/exclusion criteria not followed correctly
- Patients not withdrawn from the trial despite meeting withdrawal criteria
- Received wrong treatment, incorrect dose, or an excluded concomitant medication

The most frequent category of important protocol deviations was eligibility criteria. Overall, a small proportion of patients (~5%) in the ITT population had a protocol deviation, and therefore it's likely these had a minimal effect on the analyses or conclusions of the trial (Table 12).

Table 12: Summary of important protocol deviations in the ITT population

	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)
Any Important Protocol Deviation – n (%)	67 (4.7)	85 (6.0)	152 (5.4)
Prohibited Medications	1 (0.1)	0 (0.0)	1 (0.0)
Eligibility Criteria	60 (4.2)	77 (5.4)	137 (4.8)
Study Drug	6 (0.4)	8 (0.6)	14 (0.5)

Important protocol deviations are those thought to potentially impact the safety or efficacy analysis.
Study drug includes patients who developed withdrawal criteria but were not withdrawn or received the wrong treatment or incorrect dose.

Source: ExteNET CSR[18]

e) Limitations/Sources of Bias

Overall, the trial as originally conceived was well designed; the randomization procedure, treatment allocation, and blinding were conducted appropriately throughout the duration of the trial. However, the multiple protocol amendments that occurred and the focus of the funding request to a patient subgroup that was not pre-specified make interpretation of the trial results difficult. A number of considerations/issues and areas of uncertainty were identified, which are important when interpreting the results of the ExteNET trial, and have been summarized below:

- The trial had a number of amendments that resulted in changes to the analysis population for the primary efficacy endpoint and the follow-up duration. However, the sponsor stated that all amendments were the result of external information, including organizational change, and therefore unlikely to influence the type-1 error rate.
- Baseline characteristics were generally similar between treatment groups in the ITT population, re-consented population, and in the subgroup of patients with HR-positive status who completed trastuzumab within the past year. The treatments received prior to and during neratinib therapy are described previously. According to the CGP, the treatment history does not seem to be a source of bias nor a reason for concern regarding external validity.
- A number of subgroup analyses were performed that showed a varying magnitude of treatment effect based on clinical characteristics and treatment history. This included the target patient subgroup consistent with the Health Canada indication of neratinib and the sponsor's reimbursement request, i.e. patients with HER2-positive HR-positive breast cancer who completed trastuzumab within the past year.

However, this subgroup was not pre-specified in the SAP, and analyzed *post-hoc*. Results for all subgroups should be considered exploratory and hypothesis generating since these analyses were outside of the statistical testing hierarchy and therefore no formal inference can be drawn.

- The sample size of the ITT population (2840) was much less than the 3850 patients originally planned based on the hazard rate in the placebo group and annual dropout rate from similar trials. Following the implementation of Amendment 3, the change in the assumed hazard rate and annual dropout rate corresponded to an expected power of 88% with the accrual of 241 IDFS events. If any of the aforementioned variables were lower than expected, then the power of the study would consequently be lower. No formal power calculation was done for the primary analysis after Amendment 9 was implemented, as follow-up was limited to 2 years from randomization and the analysis was no longer event driven. It is unclear if the analyses done in the ITT population and various subgroups were adequately powered. However, due to the much lower number of IDFS events at 2 years (173 total, 106 in placebo, 67 in neratinib) than anticipated (241), the power is likely much lower than 88% as projected. Since the total number of IDFS events in the target subgroup at 2 years was 81 (55 in placebo, 26 in neratinib), much lower than the ITT population, the power for this subgroup is likely even lower. Together with the lack of pre-specification and multiplicity control, these factors present a challenge in interpreting the results of all subgroup analyses, including the target subgroup relevant for this review.
- Overall, the outcomes included in the trial were clinically relevant. The primary efficacy endpoint, IDFS, while considered an acceptable surrogate endpoint for approval in adjuvant breast cancer trials, is not consistent with the STEEP definition. Secondary primary non-breast invasive cancer, a criterion in the STEEP definition, was excluded from the definition of IDFS. However, the CGP indicated that the modified definition of IDFS used in the ExteNET trial was acceptable. HRQoL was assessed using a breast cancer specific scale (FACT-B) and a generic scale (EQ-5D); however, these scales are not specific to assess diarrhea, a major AE associated with neratinib. The FDA report identified a number of limitations associated with the overall FACT-B score; including decreased responsiveness, lack of adequate discrimination between levels of severity, and the use of broad items – all of which makes the composite score difficult to interpret. The HRQoL outcomes were assessed for 12 months only; however, this was likely done to assess the effects on patients' QoL over the treatment period. The CGP indicated that long-term safety profile of neratinib is not known.
- Per the intervention schedule, patients were subjected to 6 tablets a day for 12 months. Although the median compliance rate was 100% in both groups, it was noted that the minimum compliance rate in the neratinib group was approximately 18% which indicates considerable variability in patient compliance. The high compliance rate may not extend to the patient population in real-world practice given the high pill burden associated with neratinib treatment.
- The SAP was generally sound and appropriately conducted. However, with the exception of the primary efficacy endpoint (2-year IDFS), none of the efficacy outcomes were controlled for multiplicity. OS is planned to be tested (event driven) in a pre-specified hierarchy following the statistical significance of the 2-year IDFS primary analysis. Therefore, results of secondary outcomes and sensitivity analyses should be interpreted with caution.

- A greater proportion of patients in the neratinib group discontinued treatment as well as the study at 2 years compared with the placebo group (38.9% versus 17.1% and 22.9% versus 16.7%, respectively). The greater rate of treatment discontinuation and dropout in the neratinib group was primarily due to AEs and subject request. There is a potential risk of unblinding in the neratinib group resulting from the higher incidence of AEs (specifically diarrhea) which can result in detection bias in favour of neratinib; the extent potential unblinding affecting outcome assessment is unclear. The disproportionate treatment discontinuation and study dropout may also bias the 2-year results if the reason for discontinuation/dropout is related to the treatment (exposure) and outcomes. However, there is no evidence to suggest that the discontinuation/dropout was due to or resulted in disease recurrence. Therefore, the effect estimates obtained are unlikely to be biased, although a lack of precision may result from the fewer patients in the at-risk set. A number of sensitivity analyses were performed to address the imbalance resulting from early and disproportionate dropouts in the neratinib group – all showed consistent results with the primary analysis.
- A total of 74.5% patients provided re-consent to continue the trial for the extended period. Since these patients by definition did not have an event or die from any causes, analyses conducted solely in the re-consented population would be affected by immortal time bias. However, the 5-year analyses were also done in the ITT population by censoring patients who did not re-consent at their last physical examination if disease recurrence did not occur within the first two years of follow-up. The sponsor indicated this was done to minimize selection bias resulting from excluding non-reconsented patients. Within the re-consented population, there were fewer patients in the neratinib group. The effect of this imbalance on the 5-year results is unclear, and a lack of precision may result due to fewer patients in the at-risk set.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

IDFS in in the ITT Population

Results from the primary analysis are shown in Table 13 and a K-M plot is presented in Figure 4. Patients in the neratinib group had statistically significantly fewer IDFS events compared with patients in the placebo group at 2 years and 28 days of follow-up (67 versus 106 events; stratified hazard ratio=0·66, 95% CI: 0·49, 0·90; 1-sided p-value=0·004). The 2-year IDFS rate was 94.2% in the neratinib group and 91.9% in the placebo group, with an estimated absolute difference of 2.3%. Of the IDFS events, distant recurrence constituted the most frequent site of disease recurrence, with 3.6% and 5.0% patients in the neratinib and placebo groups, respectively.

For the primary analysis, the number of patients followed for 24 months was relatively low in each group, with 662 (47%) patients in the neratinib group and 704 (50%) patients in the placebo group. Using additional data at two later data cut-off dates (April 2016 and March 2017), the number of patients with at least 24-month follow-up was increased, and re-analyses of the primary efficacy endpoint were done. Results were consistent with the primary analysis (data not presented).

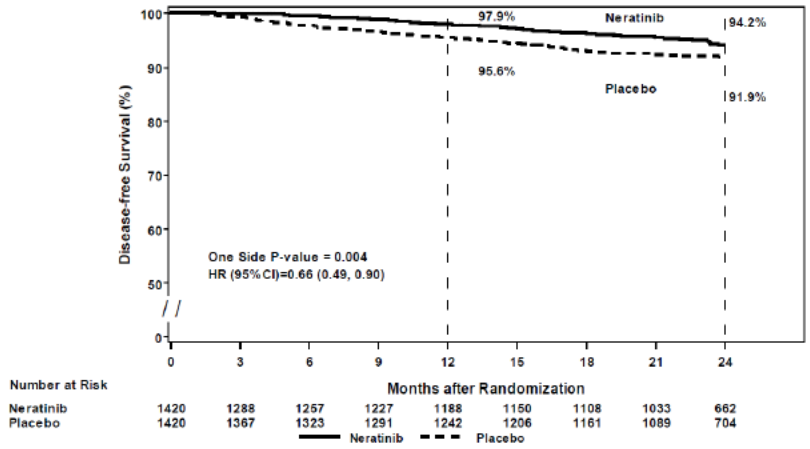
Table 13: Primary analysis of 2-year IDFS in the ITT population

IDFS Events	Neratinib N=1420	Placebo N=1420
Total IDFS Events	67 (4.7)	106 (7.5)
Local/Regional Invasive Recurrence	8 (0.6)	25 (1.8)
Invasive Ipsilateral Breast Tumor Recurrence	4 (0.3)	4 (0.3)
Invasive Contralateral Breast Cancer	2 (0.1)	5 (0.4)
Distant Recurrence	51 (3.6)	71 (5.0)
Death from Any Cause	2 (0.1)	1 (0.1)
Patients Censored	1353 (95.3)	1314 (92.5)
Kaplan-Meier Estimate	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)
Stratified Hazard Ratio	0.66 (0.49, 0.90)	
Stratified log-rank p-value (1-sided)	0.004	

Abbreviations: IDFS = invasive disease-free survival; ITT = intention to treat

Source: FDA report[20]

Figure 4: Kaplan-Meier plot of 2-year IDFS in the ITT population



Abbreviations: IDFS = invasive disease-free survival; ITT = intention to treat; HR = hazard ratio

Source: EMA report[22]

Extended 5-year IDFS in the ITT Population

Data for the analysis of 5-year IDFS are presented in Table 14 and the corresponding K-M plot is given in

Figure 5. Briefly, 279 patients had an IDFS event at the end of the 5-year period: 116 (8.2%) and 163 (11.5%) in the neratinib and placebo groups, respectively. The corresponding 5-year IDFS rate was higher in the neratinib group compared to the placebo group (90.2% and 87.7%, respectively; absolute difference of 2.5%), representing a 27% reduction in the risk of disease recurrence or death (hazard ratio=0.73; 95% CI: 0.57, 0.92; stratified 1-sided nominal log-rank test p=0.004). An interim 5-year analysis was done based on an earlier data cut-off date, April 2016, with results similar to the final analysis (data not presented).

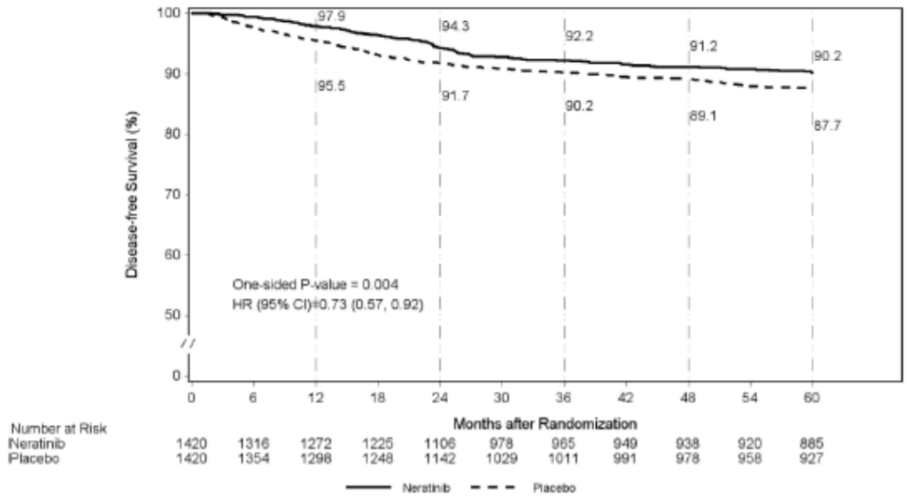
Table 14: Comparison of 5-year IDFS in the ITT population

IDFS Events	Neratinib N=1420	Placebo N=1420
Total IDFS Events	116 (8.2)	163 (11.5)
Local/Regional Invasive Recurrence	12 (1)	35 (2)
Invasive Ipsilateral Breast Tumour Recurrence	5 (<1)	7 (1)
Invasive Contralateral Breast Cancer	4 (<1)	11 (1)
Distant Recurrence	91 (6)	111 (8)
Death without previous recurrence	4 (<1)	5 (<1)
Patients Censored	1304 (91.8)	1257 (88.5)
Kaplan-Meier Estimate	90.2 (88.3, 91.8)	87.7 (85.7, 89.4)
Stratified Hazard Ratio	0.73 (0.57, 0.92)	
Stratified log-rank p-value (1-sided)	0.004	

Abbreviations: IDFS = invasive disease-free survival; ITT = intention to treat

Source: EMA report[22]

Figure 5: Kaplan-Meier plot of 5-year IDFS in the ITT population



Abbreviations: IDFS = invasive disease-free survival; ITT = intention to treat; HR = hazard ratio

Source: EMA report[22]

Subgroup Analyses

Subgroups analyses relevant for this review are described below.

Analysis of Primary Efficacy Endpoint in Subgroup of HR-positive Patients who Completed Trastuzumab in the Past Year

Data for the patient subgroup relevant to this review, i.e. patients with HR-positive breast cancer who completed trastuzumab within the past year, were reported for both 2- and 5-year IDFS. The 2-year IDFS rate was 4.5% higher in the neratinib group compared with the placebo group, corresponding to a 51% reduction in the risk of disease recurrence or death (hazard ratio=0.49; 95% CI: 0.30, 0.78). The clinical benefit of neratinib in this subgroup was consistent at the 5-year follow-up, with a hazard ratio of 0.58 (95% CI: 0.41, 0.82), which translated to a 5.1% difference between treatment groups. Results for this subgroup analysis are presented in Table 15 and corresponding K-M plots are given in Figure 6.

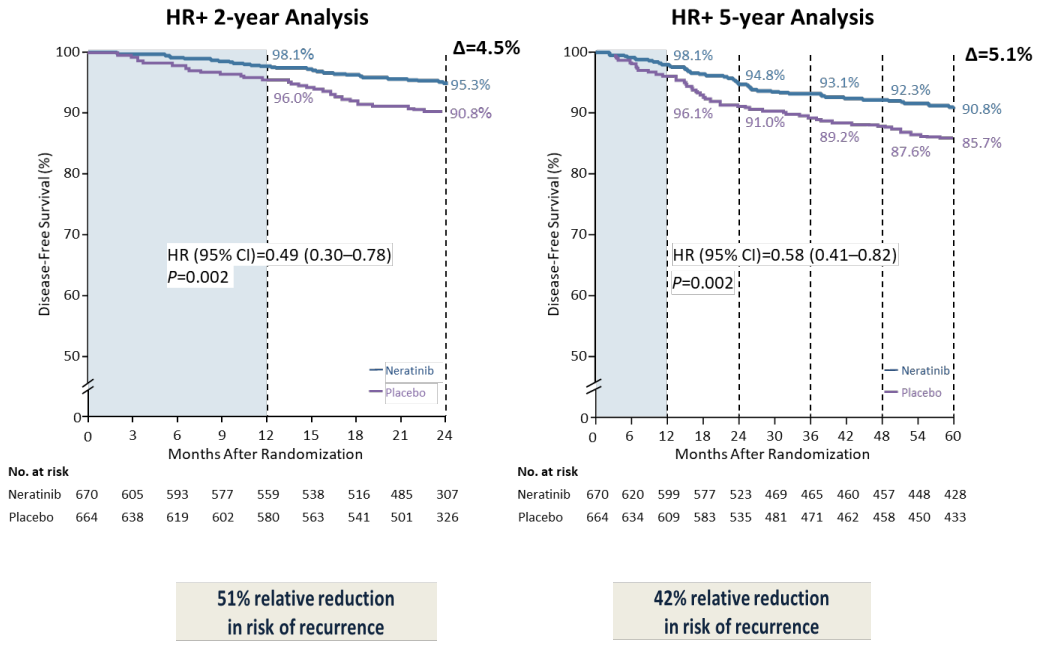
Table 15: Results of IDFS in HR-positive patients who completed trastuzumab in the past year

Endpoint	Subgroup	Number of events by 24 months N = 1334		K-M estimate (95% CI)		Unstratified hazard ratio 95% CI
		Neratinib N=670	Placebo N=664	Neratinib	Placebo	
2-year IDFS	HR-positive and ≤1 year from completion of prior trastuzumab	26 (1.9)	55 (4.1)	95.3 (93.1,96.7)	90.8 (88.2,92.9)	0.49 (0.30, 0.78)
5-year IDFS	HR-positive and ≤1 year from completion of Prior trastuzumab	51 (3.8)	89 (6.7)	90.8 (NR)	85.7 (NR)	0.58 (0.41, 0.82)

Abbreviations: CI = confidence interval; IDFS = invasive disease-free survival; ITT = intention to treat; HR = hormone receptor; NR = not reported

Source: EMA report[22] and Sponsor's Clinical Summary[23]

Figure 6: K-M plots of IDFS in HR-positive patients who completed trastuzumab in the past year



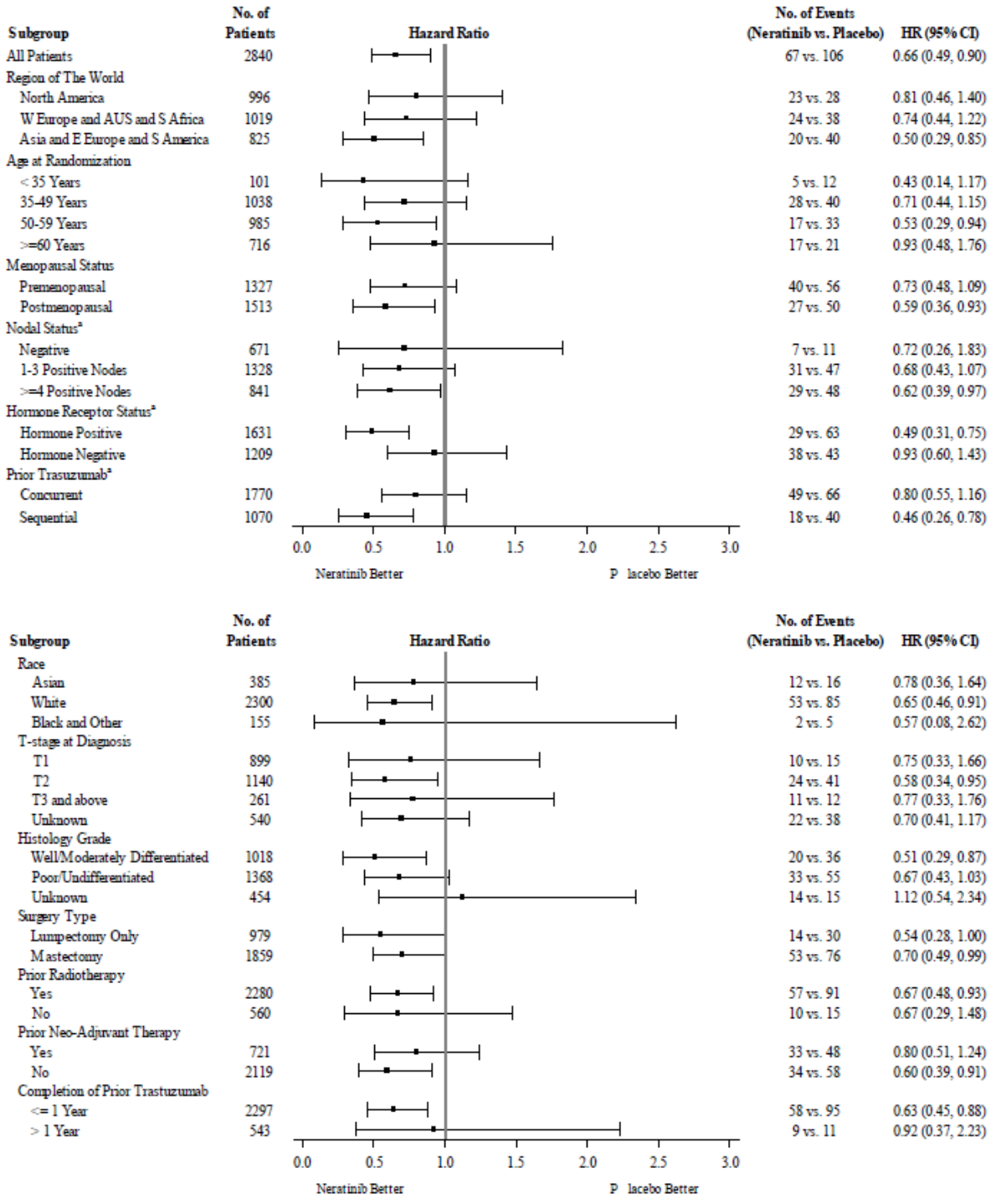
Abbreviations: CI = confidence interval; IDFS = invasive disease-free survival; ITT = intention to treat; HR = hormone receptor

Source: Sponsor's Clinical Summary[23]

Subgroup Analyses of IDFS by Baseline Characteristics in the ITT Population

Figure and Figure 8 present results of 2-year and 5-year IDFS, respectively, by baseline characteristics. For a number of pre-specified subgroups, the results at 2 and 5 years showed a benefit towards treatment with neratinib (hazard ratio <1; 95% confidence interval did not contain the null value of 1 for HR positive, T2 disease, well/moderately differentiated histology, ≥4 nodes, completion of trastuzumab ≤ 1 year, prior radiotherapy). However, at 5 years, tests for interaction showed no statistically significant differences among categories of any subgroup examined (results of interaction testing at 2 years were not reported). It is unclear if the subgroup results represent true effects as these analyses were not adjusted for multiplicity and some groups were likely underpowered; therefore, these results should be interpreted with caution.

Figure 7: Forest plot of 2-Year IDFS by subgroup in the ITT population



[a] From stratification factor

Abbreviations: IDFS = invasive disease-free survival; ITT = intention to treat; HR = hazard ratio

Source: ExteNET CSR[18]

Figure 8: Forest plot of 5-year IDFS by subgroups in the ITT population

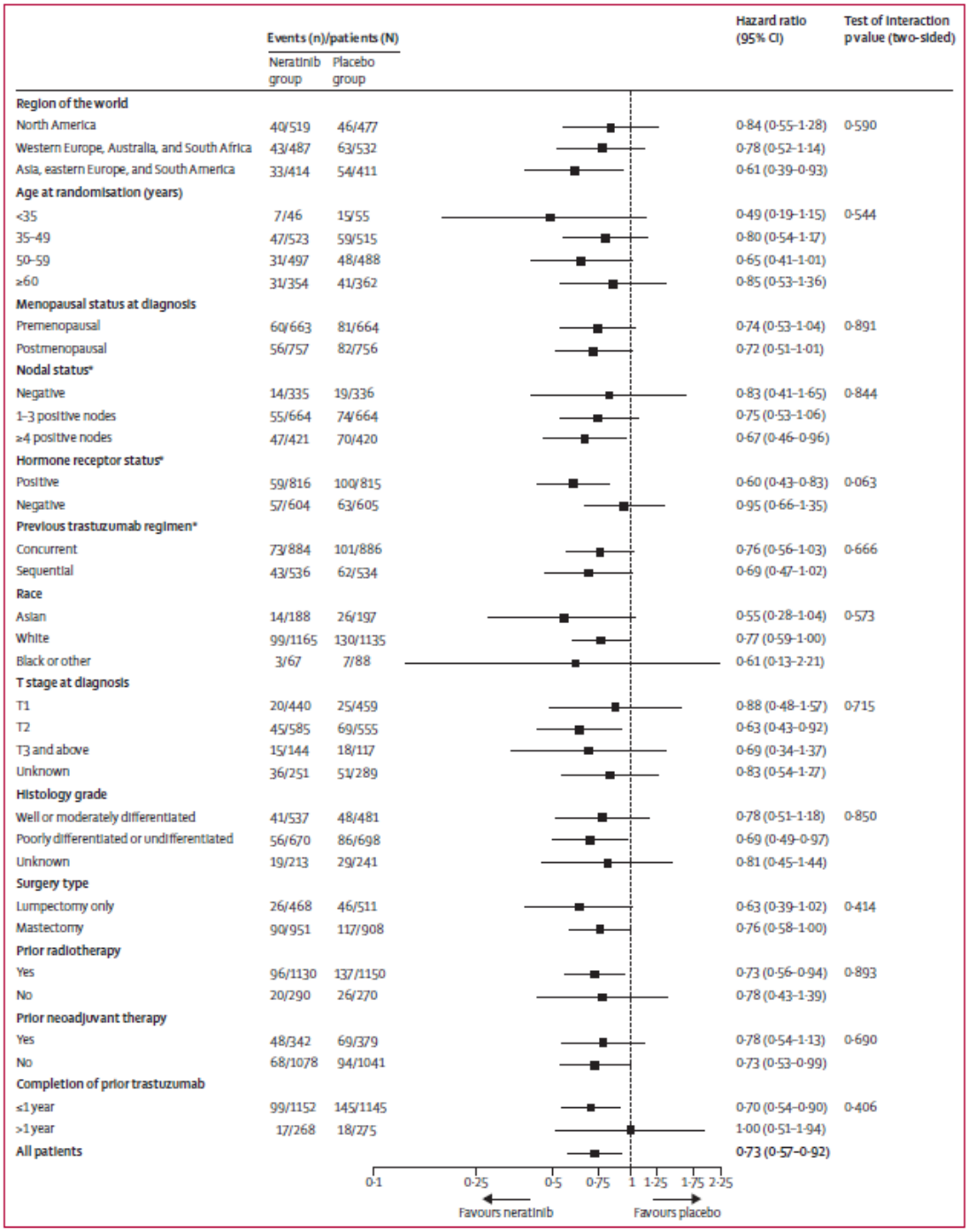


Figure 3: **Subgroup analysis of invasive disease-free survival in the intention-to-treat population**
The vertical dashed line indicates a hazard ratio of 1·00—the null hypothesis value. Error bars represent 95% CIs. *Stratification factor.

Abbreviations: IDFS = invasive disease-free survival; ITT = intention to treat; HR = hazard ratio

Source: Reprinted from The Lancet Oncology, Vol.18 number 12, Martin M, Holmes FA, Ejlertsen B, et a, 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, Pages No.1688-1700, Copyright (2017), with permission from Elsevier.[3]

Secondary Efficacy Endpoints in the ITT Population

Analyses of secondary efficacy endpoints at 2 and 5 years are summarized in Table 16 and Table 17, respectively. As these analyses were not controlled for type-1 error, the results should be considered descriptive.

Overall, neratinib showed benefits in DFS-DCIS, DDFS, TTDR, and CNS recurrence compared with placebo at 2 years but only DFS-DCIS demonstrated a statistically significant benefit (94.2% versus 91.3%; stratified hazard ratio=0·61, 95% CI: 0·45, 0·83; nominal p-value=0·001).
At 5 years, neratinib resulted in an improvement in DFS-DCIS, DDFS, and TTDR compared with placebo (stratified hazard ratios of 0.71, 0.78, and 0.79, respectively, nominal p-value < 0.05 for all outcomes). The number of CNS recurrences observed was low; and therefore, no inferences about treatment benefit can be made.

Table 16: Summary of results from 2-year secondary endpoint analyses in the ITT Population

Endpoint	iDFS Rate at 24 months[a] (%, 95% CI)		Stratified HR (95% CI)	Stratified log-rank test p-value[b] (two-sided)
	Neratinib	Placebo		
DFS-DCIS	94.2 (92.6, 95.4)	91.3 (89.6, 92.7)	0.61 (0.45, 0.83)	0.001
DDFS	95.3 (93.9, 96.4)	94.0 (92.6, 95.2)	0.74 (0.52, 1.05)	0.094
TTDR	95.5 (94.1, 96.6)	94.2 (92.8, 95.3)	0.73 (0.51, 1.04)	0.087
CNS Recurrence Cumulative Incidence Estimate	0.92 (0.49, 1.59)	1.16 (0.68, 1.87)	NA	0.548[c]

[a] Kaplan-Meier estimate unless otherwise noted
[b] Nominal p-value without adjustment for multiple comparisons
[c] By stratified Gray's test

Abbreviations: CNS = central nervous system; DCIS = ductal carcinoma *in situ*; (D)DFS = (distant) disease-free survival; ITT = intention to treat; HR = hazard ratio; TTDR = time to disease recurrence.

Source: FDA report[20]

Table 17: Summary of results from 5-ear secondary endpoint analyses in the ITT population

	Estimated Event-Free Survival Rate[a]			
	Neratinib (N=1420)	Placebo (N=1420)	HR (95% CI)[b]	P-Value[c]
DFS-DCIS	89.7%	86.8%	0.71 (0.56, 0.89)	0.002
DDFS	91.6%	89.9%	0.78 (0.60, 1.01)	0.032
TTDR	91.8%	90.3%	0.79 (0.60, 1.03)	0.039
CNS Recurrence: cumulative incidence estimate	1.30%	1.82%	NA	0. 166

a Event-free rates for all endpoints except for CNS recurrence for which cumulative incidence is reported.
b Stratified Cox proportional hazards model.
c Descriptive P-value (1-sided)

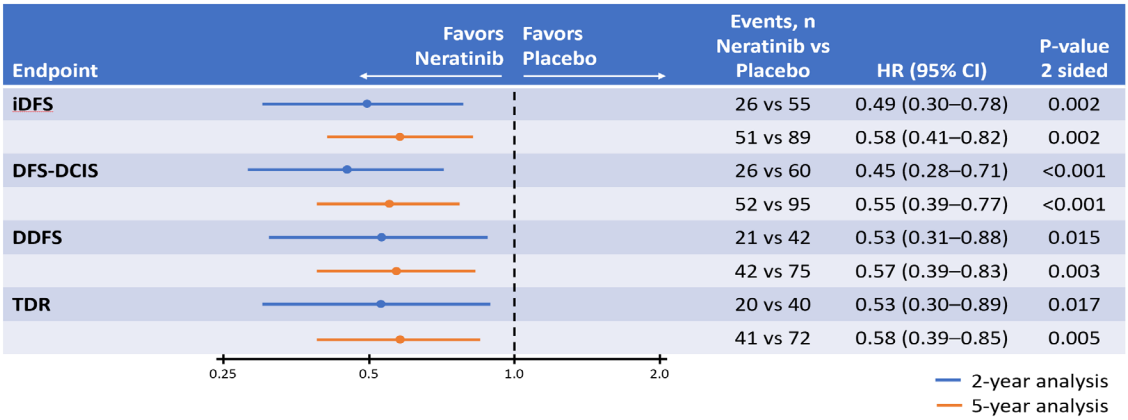
Abbreviations: CNS = central nervous system; DCIS = ductal carcinoma *in situ*; (D)DFS = (distant) disease-free survival; ITT = intention to treat; HR = hazard ratio; TTDR = time to disease recurrence.

Source: EMA report[22]

Analysis of Secondary Efficacy Endpoints in HR-positive Patients who Completed Trastuzumab in the Past Year

Among patients with HR-positive breast cancer who completed trastuzumab within the past year, both 2- and 5-year DFS-DCIS, DDFS, and TTDR appeared improved in the neratinib group compared with the placebo group. Results are shown in Figure 9. As previously noted, efficacy analyses in this patient subgroup were not pre-specified, conducted post-hoc, and were not adjusted for multiplicity; therefore, they should be interpreted with caution.

Figure 9: Results of efficacy endpoints in HR-positive patients who completed trastuzumab in the past year



Endpoint	Events, n Neratinib vs Placebo	HR (95% CI)	P-value 2 sided
iDFS	26 vs 55	0.49 (0.30–0.78)	0.002
	51 vs 89	0.58 (0.41–0.82)	0.002
DFS-DCIS	26 vs 60	0.45 (0.28–0.71)	<0.001
	52 vs 95	0.55 (0.39–0.77)	<0.001
DDFS	21 vs 42	0.53 (0.31–0.88)	0.015
	42 vs 75	0.57 (0.39–0.83)	0.003
TDR	20 vs 40	0.53 (0.30–0.89)	0.017
	41 vs 72	0.58 (0.39–0.85)	0.005

Abbreviations: DCIS = ductal carcinoma *in situ*; (I/D)DFS = (invasive/distant) disease-free survival; ITT = intention to treat; HR = hazard ratio; TDR = time to disease recurrence

Source: Sponsor's Clinical Summary[23]

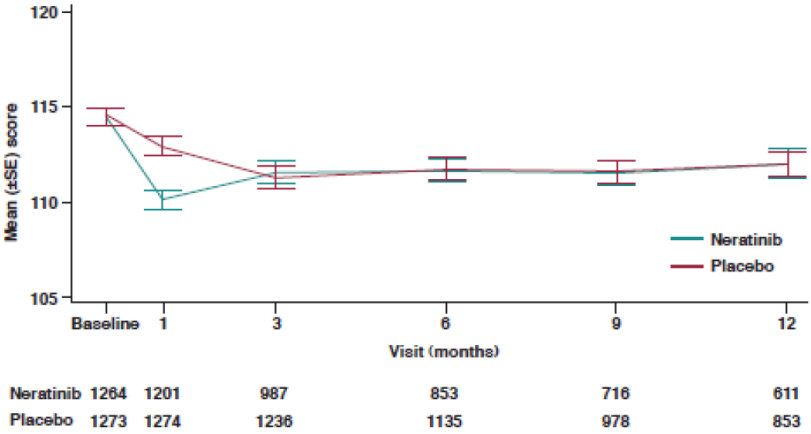
Health-related Quality of Life in the ITT Population

FACT-B

A total of 2407 patients (84.8%) completed FACT-B questionnaires (neratinib, N=1171; placebo, N=1236) at least once post-baseline, and the questionnaire completion rates were balanced between treatment groups at all timepoints (data not presented). The questionnaire completion rate was approximately 80% or more until month 9, after which the completion rate was lower (approximately 70%). HRQoL data collection ceased in October 2011 (protocol Amendment 9).

Overall, FACT-B scores decreased in both treatment groups by year 1 (Figure 10). The most pronounced difference between-groups occurred at month 1 and favoured treatment with placebo over neratinib (1.7 point versus 4.6 points, adjusted mean difference -2·9 [95% CI -3·7 to -2·0]). The initial decrease in QoL as reported by FACT-B is consistent with the GI AEs (specifically diarrhea) reported during the first few months following neratinib treatment (details below). At month 3 and thereafter, there were decreases in mean scores of about 3 points from baseline in both groups; however, there was no noticeable difference between-treatment groups. Considering the individual scale scores, physical well-being showed the largest difference between the two groups in the first month and over time, whereas functional well-being, emotional well-being, social/family well-being, and cancer-specific subscales showed negligible differences. The MCID was not reached in either group at any time-point for the total or individual scale scores of FACT-B. A similar pattern was observed for the FACT-G Total Score (data not presented).

Figure10: Mean FACT-B Total Scores Over Time in the ITT Population



Abbreviations: FACT-B = Functional Assessment of Cancer Therapy – Breast; ITT = intention-to-treat

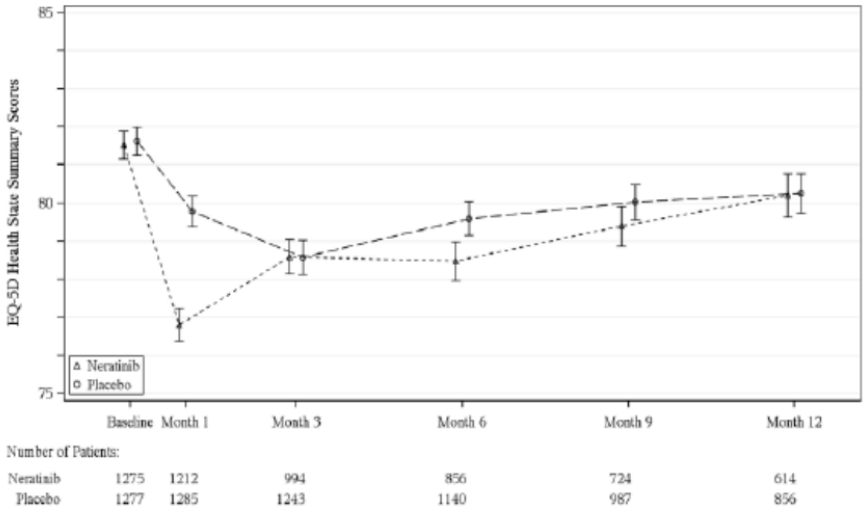
Source: Reprinted from The Lancet Oncology, Vol.17 number3, Chan A, Delaloge S, Holmes FA, et al., Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial., Pages No.367-377, Copyright (2016), with permission from Elsevier.[2]

EQ-5D

A total of 2427 patients (85.5%) had at least one EQ-5D (neratinib, N = 1186; placebo, N = 1241) measurement post-baseline, and the questionnaire completion rates were balanced between treatment groups at all timepoints (data not presented). Similar to the FACT-B score, the questionnaire completion rate for EQ-5D was approximately 80% or more until month 9, following which the rate dropped to approximately 70%.

Over time there was a decrease in the EQ-5D health state scores (VAS and index) in both treatment groups (Figure 11 and Figure 12). The mean EQ-5D VAS scores decreased from baseline by 2.3 points in the placebo group at month 1 and by 4.9 points in the neratinib group (adjusted mean difference –2·7 [–3·7 to –1·7]). Thereafter, the score rebounded closer to baseline values, with a decrease in mean scores of about 2 to 3 points by month 12. A similar pattern was observed in the EQ-5D index score (adjusted mean difference –0.02 [–0.03 to –0.01]). The MCID was not reached for either score at any assessment timepoint. The initial decrease in QoL as reported by the EQ-5D is consistent with the GI AEs (specifically diarrhea) reported during the first few months following neratinib treatment.

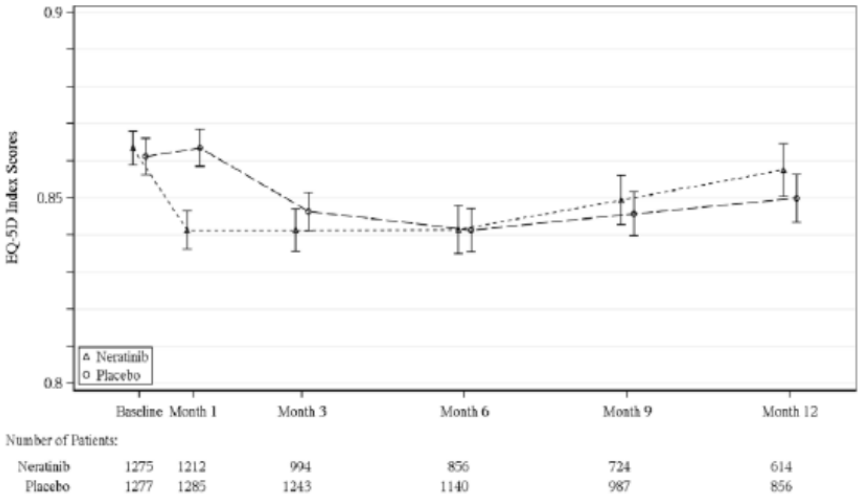
Figure 11: Average EQ-5D health state summary scores over time in the ITT Population



Abbreviations: EQ-5D = Euro QoL-5-dimension; ITT = intention-to-treat

Source: EMA report[22]

Figure 12: Average EQ-5D index scores over time in the ITT population



Abbreviations: EQ-5D = Euro QoL-5-dimension; ITT = intention-to-treat

Source: EMA report[22]

Results of Sensitivity Analyses

A number of sensitivity analyses were conducted to assess the influence of other factors that could potentially affect the interpretation of the primary analysis results. These included missed visits, use of other systemic anti-cancer therapy, and early drop-outs. Two additional sensitivity analyses of IDFS were performed: (i) one excluding all patients from study sites with a high rate of early dropout (< 10%), and (ii) one including only patients

from sites that had a high rate of complete follow-up (≥ 90%). Finally, a sensitivity analysis was done by changing the censoring rule per the original SAP, whereby all recurrent disease events and deaths occurring within 2 years and 28 days post randomization were regarded as events. Notably, this censoring rule was later updated in the final SAP per FDA request and considered a sensitivity analysis. Overall, results from all these sensitivity analyses showed the robustness of the primary analysis results, with consistent hazard ratios and 95% CIs across the different scenarios. A summary of the key sensitivity analyses is shown in Table 18.

Results from the sensitivity analysis that examined the effect of early dropouts (patients censored at < 3 months) on the primary analysis results showed an average of 9 (range 1-22) additional IDFS events were observed in the resampled population (HR of 0.69 and a standard deviation of 0.03). Additionally, baseline demographic and disease characteristics and prior anti-cancer therapy were similar for patients who dropped out with ≤ 3 months of follow-up compared to patients who were followed up for > 3 months.

Table 18: Sensitivity analyses – effects of follow-up period, missed visits, use of systemic anti-cancer therapy, and protocol compliance on IDFS (ITT population)

Population	Number of Events by 24 Months		K-M Estimate 24-month Rate % (95% CI)		Stratified Hazard Ratio (95% CI)[a]	Stratified Log Rank Test p-value (1-sided)[a]
	Neratinib	Placebo	Neratinib	Placebo		
All Events up to 2 Year + 28 Days	70	109	93.9 (92.4,95.2)	91.6 (90.0,93.0)	0.67 (0.50,0.91)	0.005
Patients Missing 2 Visits (6 Month Window)	65	105	94.4 (92.9,95.6)	91.9 (90.3,93.3)	0.65 (0.47,0.88)	0.003
Patients with Systemic Anti-cancer Therapy	66	104	94.2 (92.7,95.4)	92.0 (90.4,93.4)	0.67 (0.49,0.90)	0.005
Site Early Dropout Rate <10%	57	88	94.1 (92.4,95.4)	91.6 (89.7,93.1)	0.66 (0.47,0.93)	0.008
Site Completed Follow-up ≥90%	43	67	93.9 (91.8,95.4)	91.3 (89.1,93.1)	0.69 (0.47,1.01)	0.028

[a] Compared with placebo based upon a Cox proportional hazards model stratified by factors used in randomization.

Abbreviations: ITT = intention-to-treat; K-M = Kaplan-Meier

Source: EMA report[22]

Harms Outcomes

A brief summary of treatment-emergent adverse events (TEAEs) that occurred in the ITT population (2-year data cut-off date) in the ExteNET trial is shown in Table 19. Safety results were not reported separately for the target subgroup (HR-positive patients who completed trastuzumab within the past year). A TEAE(s), herein referred to as AE(s), was defined as an AE that occurred or worsened on or after the first administration of study drug and up to 28 days after last dose.

Overall, the majority of patients reported at least one AE (93.3%). Compared to placebo, more patients in the neratinib group experienced AEs, grade ≥ 3 AEs, SAEs, and AEs leading to treatment and/or study discontinuation, dose reduction and/or hold.

Table 19: Overall summary of treatment-emergent AEs - safety population

	Neratinib (N=1408)	Placebo (N=1408)	Total (N=2816)
Any TEAE	1387 (98.5)	1240 (88.1)	2627 (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	1353 (96.1)	805 (57.2)	2158 (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 Hospitalization	93 (6.6)	75 (5.3)	168 (6.0)
TEAE Leading to Dose Hold	629 (44.7)	187 (13.3)	816 (29.0)

Adverse events were coded using the MedDRA dictionary V17.0; Grade is based on CTCAE 3.0.

Abbreviations: SAE = serious adverse event; TEAE = treatment emergent adverse event

Source: ExteNET CSR[18]

Error! Reference source not found. 20 summarizes the most frequently reported (≥ 10% incidence) AEs, categorized by severity. Most notably, the incidence of grade 1-3 diarrhea occurred in a much greater proportion among neratinib-treated patients than patients receiving placebo. Diarrhea led to neratinib dose reductions in 372 (26%) patients in the neratinib group and eight (1%) patients in the placebo group; hospital admission in 20 (1%) versus one (<1%) patient; and drug discontinuation in 237 (17%) patients versus three (<1%) patients (data not presented). Patients in the neratinib group also reported more grade 1-2 fatigue, vomiting, abdominal pain and upper abdominal pain, rash, decreased appetite, and muscle spasms compared with patients in the placebo group.

Table 20: AEs with ≥ 10% incidence - safety population

	Neratinib group (n=1408)			Placebo group (n=1408)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
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
Headache	269 (19%)	8 (1%)	0	269 (19%)	6 (<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
Dizziness	143 (10%)	3 (<1%)	0	125 (9%)	3 (<1%)	0
Arthralgia	84 (6%)	2 (<1%)	0	158 (11%)	4 (<1%)	0

Source: Reprinted from The Lancet Oncology, Vol.17 number3, Chan A, Delaloge S, Holmes FA, et al., Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial., Pages No.367-377, Copyright (2016), with permission from Elsevier.[2]

Table 21 summarizes the most frequently reported (n ≥ 3 incidence) SAEs by treatment group. The SAEs with the highest incidence in the neratinib group were GI or hepatic in nature.

Table 21: SAEs occurring in ≥3 patients - safety population

Preferred term	Neratinib N=1408 n (%)	Placebo N=1408 n (%)
Diarrhoea	22 (1.6)	1 (0.1)
Vomiting	12 (0.9)	1 (0.1)
Dehydration	9 (0.6)	1 (0.1)
Nausea	4 (0.3)	1 (0.1)
ALT increased	4 (0.3)	0
AST increased	4 (0.3)	0
Cellulitis	6 (0.4)	4 (0.3)
Erysipelas	5 (0.4)	0
Fatigue	3 (0.2)	0
Pulmonary embolism	3 (0.2)	3 (0.2)
Non-cardiac chest pain	3 (0.2)	0
Renal failure acute	3 (0.2)	0
Syncope	3 (0.2)	2 (0.1)

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase

Source: EMA report[22]

Other notable AEs occurring during the 2-year analysis included cardiac toxicity, which was reported for 148 (10.5%) patients in the neratinib group and 182 (12.9%) patients in the placebo group; of which ≥ grade 3 events were reported for 21 (1.5%) and 7 (0.5%) patients, respectively. QT prolongation occurred in 49 (3%) patients receiving neratinib and 93 (7%) patients receiving placebo and decreases in left ventricular ejection fraction (≥ grade 2) occurred in 19 (1%) and 15 (1%) patients, respectively. The incidence of AEs indicative of hepatotoxicity was 12.4% (≥ grade 3: 1.8%) for the neratinib group compared with 6.6% (≥ grade 3: 0.6%) for the placebo group (data not presented). Second cancers (i.e. neoplasms benign, malignant, and unspecified, including cysts and polyps) were observed in 11 (1%) patients in each group. Results from the 5-year safety analysis suggested no evidence of increased long-term toxicity, including symptomatic cardiac toxicity, or second primary malignancies in the neratinib group compared with the placebo group.

In part A of the trial, a total of seven (< 1%) deaths occurred after treatment discontinuation, four and three patients in the neratinib and placebo groups, respectively. The causes of death were unknown (n=2), cancer/metastases in other sites (n = 3), brain hemorrhage (n=1), and myocardial infarction (n=1). None of the deaths were attributed to study drug. At the end of the 5-year analysis, a total of 121 deaths were reported in both treatment groups resulting from disease progression (n=102) or other reasons (n=19).

6.4 Ongoing Trials

No ongoing trials meeting the selection criteria of the review were identified.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were identified during development of the review.

8 COMPARISON WITH OTHER LITERATURE

The ExteNET trial reported diarrhea to be the main toxicity associated with neratinib treatment. Diarrheal episodes were particularly frequent in the early course of treatment. Therefore, a structured prophylactic regimen to minimize diarrhea is recommended for 1-2 cycles. According to the product monograph, antidiarrheal prophylaxis is recommended during the first 2 cycles (56 days) of treatment and should be initiated with the first dose of neratinib.[1]

Patients in the ExteNET trial were not required to receive antidiarrheal prophylaxis. CONTROL is an ongoing, open-label, phase II trial designed to assess three prophylactic regimens to manage diarrheal episodes in patients treated with neratinib. The sponsor provided a conference poster with preliminary findings from this trial. Given the prescription of neratinib will likely include a prophylactic agent for diarrhea, the CGP identified this study as being relevant, even though it did not meet the selection criteria of the systematic review.

CONTROL

Summary of the Trial

a) Study design

CONTROL (PUMA-NER-6201)[4] is an international, open-label, sequential-cohort, phase II trial that investigated the incidence and severity of diarrhea in early-stage HER2-positive breast cancer patients receiving neratinib with loperamide alone and in combination with either budesonide (an anti-inflammatory treatment) or colestipol (a bile acid sequestrant treatment), who have previously undergone a course of trastuzumab therapy in the adjuvant setting.

b) Study Population

The CONTROL trial enrolled patients using similar eligibility criteria to the ExteNET trial. Eligible patients were ≥ 18 years of age and had histologically confirmed stage I-IIIc breast cancer, documented HER2 overexpression or amplification, no evidence of local/regional recurrence or metastatic disease, an ECOG PS of ≤ 1, and completed one year of prior trastuzumab-based adjuvant therapy given > 2 weeks and ≤ 1 year from enrollment. Exclusion criteria included having a major surgery < 30 days, significant GI, respiratory, or cardiac disease, and any concomitant cancer therapy. Endocrine therapy and other prior HER2-directed therapy, including pertuzumab and trastuzumab emtansine (TDM-1), were permitted.

The baseline characteristics of included patients are summarized in Table 22. A total of 321 patients were enrolled from 41 sites. The loperamide, budesonide, and colestipol cohorts consisted of 137, 64, and 120 patients, respectively. The median age of patients ranged between 49 and 53 years. Almost half of patients were disease stage II, and over 70% had a HR-positive tumour. Most patients received trastuzumab and taxanes. Notably, 40% patients in the loperamide cohort received prior pertuzumab, compared with approximately 60% patients in the budesonide and colestipol cohorts. As of the data cut-off date, all patients (100%) in the loperamide cohort had completed or prematurely discontinued neratinib treatment, as opposed to 73% and 21% of patients in the budesonide and colestipol cohorts, respectively; the median duration of neratinib treatment in the three cohorts was 11.5, 11.9, and 3.7 months, respectively.

Table 22: Baseline characteristics

Variable	CONTROL			ExteNET
	Loperamide cohort (n=137)	Budesonide cohort (n=64)	Colestipol cohort (n=120)	(n=1420)
Female, %	100	100	98	100
Median age (range), years	53 (30–86)	49 (29–78)	53 (26–78)	52 (25–83)
Tumor stage at diagnosis,[a] %				
I	28.5	25.0	16.7	9.8
IIA, B	54.7	46.9	46.7	42.0
IIIA, B, C	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
Missing	0	0	<1	0
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	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)

ER, estrogen receptor; PR, progesterone receptor.

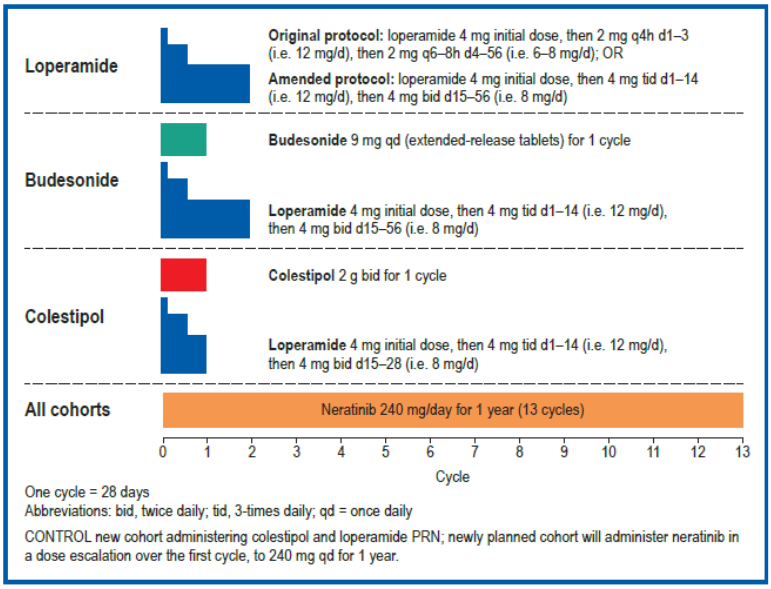
Source: CONTROL trial poster.[4]

c) Intervention

The treatment schedule of the three cohorts in the CONTROL trial is shown in Figure 13. Patients received oral loperamide for 1 or 2 cycles, loperamide plus budesonide for 1 cycle, or loperamide plus colestipol for 1 cycle. Each cycle was 4 weeks in length. All patients received additional loperamide (≤16 mg/day) as needed after the completion of their treatment schedule.

Patients who were unable to tolerate any of the three treatment regimens due to symptomatic constipation had their loperamide dose held until after the first bowel movement and then resumed at a reduced dose. Any treatment-emergent diarrhea in patients was managed with neratinib dose modifications, dietetic measures and additional pharmacological treatments (diphenoxylate plus atropine, octreotide, IV fluids, antibiotics) depending on severity.

Figure 13: Treatment schedules by cohort



Source: CONTROL trial poster.[4]

d) Outcomes

The primary endpoint of the trial was the incidence of grade ≥ 3 diarrhea. Secondary endpoints included the incidence of maximum-grade diarrhea, diarrhea by loperamide exposure, SAEs, and AEs of interest (not specified). HRQoL was measured using the FACT-B and EQ-5D questionnaires and were exploratory endpoints; only data for the FACT-B were published in the conference poster. No information on patient compliance for completing questionnaires was reported.

e) Statistical Analysis

Both safety and HRQoL analyses were descriptive in nature. Changes in HRQoL scores from baseline and between groups were compared with MCID from the literature. The neratinib group of the ExteNET trial, which included an analogous patient population but no protocol-specified antidiarrheal prophylaxis, was used as a historical control group.

Summary of Outcomes

Diarrheal Outcomes

The incidence of grade ≥ 3 diarrhea was lowest in the colestipol cohort (10.8% [95% CI 5.9–17.8]), followed by the budesonide cohort (26.6% [95% CI 16.3–39.1]), and the loperamide cohort (30.7% [95% CI 23.1–39.1]). In the ExteNET trial, the incidence of grade ≥ 3 diarrhea was 39.9% (95% CI 37.3–42.5). The colestipol cohort also experienced the lowest number of diarrheal episodes (including grade ≥ 2 diarrhea), cumulative duration of diarrhea (including grade ≥ 2 diarrhea), and neratinib dose modification due to diarrhea. Compared to the ExteNET trial, patients receiving loperamide prophylaxis with or without budesonide and colestipol had a reduction in the duration and severity of diarrhea, diarrheal episodes per patient, and the requirement of neratinib dose modification. Additionally, patients in the ExteNET trial had chronic grade ≥ 2 diarrheal episodes that peaked in month 1 and were still observed in months 2-12, whereas all three cohorts in the CONTROL trial had a reduction in grade ≥ 2 diarrhea during month 1 that continued through month 12. The characteristics of treatment-emergent diarrhea are summarized in Table 23.

Table23: Characteristics of treatment-emergent diarrhea

Study	CONTROL			ExteNET[3]
Variable	Loperamide (n=137)	Loperamide + budesonide (n=64)	Loperamide + colestipol (n=120)	Loperamide prn (n=1408)
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 diarrhea episodes/patient				
Any grade	2	9	2.5	8
Grade ≥2	2	3	1	3
Grade ≥3[a]	1	1	1	2
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
Hospitalization	1.5	0	0	1.4

Source: CONTROL trial poster.[4]

Other Adverse Events

Aside from diarrhea, the overall safety profile of neratinib with or without antidiarrheal prophylaxis in the ExteNET and CONTROL trial were similar (Table 24). However, there was an increase in constipation; grade 1/2 constipation was reported in 42.3%/14.6%, 62.5%/12.5%, and 53.3%/9.2% patients in the loperamide, budesonide, and colestipol cohorts, respectively (data not presented). Within the CONTROL trial, the colestipol cohort had the lowest frequency of AEs. Sepsis and urinary tract infection were the only reported grade 4 AEs and both were unrelated to study treatment; however, it was not specified whether these events applied to any particular cohort or the full population). No fatal AEs were reported.

Table 24: Most common grade ≥ 3 AEs (≥ 1% total incidence in CONTROL)

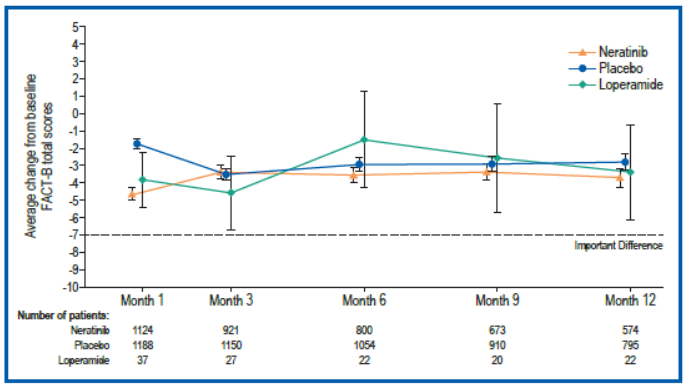
	CONTROL			ExteNET
Grade 3/4 events, %	Loperamide cohort (n=137)	Budesonide cohort (n=64)	Colestipol cohort (n=120)	Neratinib arm (n=1408)
Diarrhea	30.7	26.6	10.8	39.9
Fatigue	3.6	7.8	1.7	1.6
Vomiting	1.5	3.1	1.7	3.3
Abdominal pain	1.5	1.6	0.8	1.7
Dehydration	1.5	1.6	0.8	0.9

Source: CONTROL trial poster.[4]

Health-related Quality of Life

HRQoL, measured by FACT-B, did not appear affected in the CONTROL trial. However, baseline and post-baseline scores were not provided for all cohorts. Among 37 loperamide-treated patients, changes from baseline in FACT-B total scores were less than the MCID (7-8 points) for all time points, and the differences were resolved towards baseline values as in the ExteNET trial.

Figure 14: Mean change from baseline in FACT-B total scores in the CONTROL and ExteNET trials



Source: CONTROL trial poster.[4]

Conclusion

Overall, the study concluded that the addition of loperamide prophylaxis regimens resulted in an improved diarrheal profile. Any impact on HRQoL was short-lived and did not reach predefined clinically meaningful thresholds in the loperamide cohort. Among the antidiarrheal prophylaxis regimens, loperamide in combination with colestipol had the best toxicity profile.

A number of limitations should be noted. Only 21% of the patients in this cohort completed neratinib treatment as of the data cut-off date, as opposed to 73% and 100% patients in the budesonide and loperamide cohorts, respectively. This, in combination with the open-label nature of the trial and a lack of formal statistical tests should be considered when interpreting the results. The final analyses of the CONTROL trial with 12-month treatment completed for all patients would be beneficial in this regard, as HRQoL data were not available for most cohort patients at baseline and post-baseline.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Breast Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on neratinib for early breast cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Breast Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

Literature Search Methods

1. Literature search via Ovid platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials March 2019**, Embase** 1974 to 2019
April 29**, Ovid MEDLINE(R) ALL** 1946 to April 29, 2019

#	Searches	Results
1	(Nerlynx* or neratinib* or hki 272 or hki272 or way 177820 or way177820 or PB-272 or PB272 or JJH94R3PWB or 9RM7XY23ZS).ti,ab,ot,kf,kw,hw,rn.	1827
2	exp Breast Neoplasms/	777072
3	exp Breast/ or (breast* or mammar* or nipple*).ti,ab,kw,kf.	1161259
4	exp Neoplasms/ or (neoplas* or malignan* or carcinoma* or cancer* or tumor* or tumour* or sarcoma*).ti,ab,kw,kf.	9288919
5	2 or (3 and 4)	1032510
6	1 and 5	1202
7	6 use medall	170
8	6 use cctr	80
9	7 or 8	250
10	*neratinib/	244
11	(Nerlynx* or Neratinib* or hki 272 or hki272 or way 177820 or way177820 or PB-272).ti,ab,kw,dq.	1055
12	10 or 11	1069
13	exp breast tumor/	777072
14	exp Breast/ or (breast* or mammar* or nipple*).ti,ab,kw.	1160973
15	exp Neoplasm/ or (neoplas* or malignan* or carcinoma* or cancer* or tumor* or tumour* or sarcoma*).ti,ab,kw.	9283682
16	13 or (14 and 15)	1031902
17	12 and 16	758
18	17 use oemezd	512
19	18 not (conference review or conference abstract).pt.	267
20	9 or 19	517

21	remove duplicates from 20	342
22	18 and (conference review or conference abstract).pt.	245
23	limit 22 to yr="2014 -Current"	174
24	21 or 23	516
25	limit 24 to english language	492

2. **Literature search via PubMed**
A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#7	Search #5 AND #6	10
#6	Search publisher[sb]	524721
#5	Search #1 AND #4	169
#4	Search #2 OR #3	404221
#3	Search (Breast[Mesh] OR breast[tiab] OR breasts[tiab] OR mammar*[tiab] OR nipple*[tiab]) AND (Neoplasms[Mesh] OR neoplas*[tiab] OR malignan*[tiab] OR carcinoma*[tiab] OR cancer*[tiab] OR tumor[tiab] OR tumour[tiab] OR tumors[tiab] OR tumours[tiab] OR tumorous[tiab] OR tumourous[tiab] OR sarcoma*[tiab])	370131
#2	Search Breast Neoplasms[Mesh]	275279
#1	Search N-(4-(3-chloro-4-(2-pyridinylmethoxy)anilino)-3-cyano-7-ethoxy-6-quinolyl)-4-(dimethylamino)-2-butenamide [Supplementary Concept] OR Nerlynx*[tiab] OR neratinib*[tiab] OR hki 272[tiab] OR hki272 [tiab] OR way 177820 [tiab] OR way177820 [tiab] OR PB-272 [tiab] OR PB272[tiab] OR JJH94R3PWB [tiab] OR 9RM7XY23ZS[tiab]	259

3. **Cochrane Central Register of Controlled Trials (CENTRAL)**
(searched via Ovid)

4. **Grey literature search via:**

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Nerlynx/neratinib, breast cancer

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)

https://www.ema.europa.eu/

Search: Nerlynx/neratinib, breast cancer

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

San Antonio Breast Cancer Symposium (SABCS)
https://www.abstracts2view.com/sabcs/

Search: Nerlynx/neratinib, breast cancer— last five years

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[28]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) Mar 2019) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Nerlynx/neratinib and breast cancer.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of September 5, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[29] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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