pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Neratinib (Nerlynx)	
Submitted Reimbursement Request: For patients with human epidermal growth factor receptor 2 (HER2)-positive, hormone receptor (HR)-positive breast cancer who have completed adjuvant trastuzumab-based therapy within the past 12 months.	
Submitted By: Knight Therapeutics Inc.	**Manufactured By:** Knight Therapeutics Inc.
NOC Date: July 16, 2019	**Submission Date:** April 18, 2019
Initial Recommendation: October 3, 2019	**Final Recommendation:** December 5, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Neratinib costs $45.00 per 40 mg tablet. At the recommended dose of 240 mg (six 40 mg tablets) given orally once daily, neratinib costs $270.00 per day, $7,560.00 per 28-day course and $98,550.00 for one year.

pERC RECOMMENDATION

☐ **Reimburse**

☐ **Reimburse with clinical criteria and/or conditions***

☒ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC does not recommend reimbursement of neratinib (Nerlynx) for the treatment of patients with HER2-positive, HR-positive breast cancer who have completed trastuzumab-based therapy within the past 12 months.

The Committee made this recommendation because it was not satisfied that there is a clinically meaningful net benefit of extended adjuvant treatment with neratinib in patients with HER2-positive, HR-positive early breast cancer who have completed trastuzumab-based therapy within the past year (the subgroup for which the sponsor has submitted this request). The Committee noted that there was a high level of uncertainty around the magnitude of the invasive disease-free survival (IDFS) benefit given that the treatment effect was estimated based on a subgroup analysis of a specific subset of patients who were HR-positive and had completed trastuzumab within the past year that was not pre-specified, other limitations of the trial related to specific protocol amendments, and the lack of overall survival (OS) data (due to data immaturity) to confirm clinical benefit. pERC was uncertain whether neratinib adequately addresses the need for more effective therapies in patients at higher risk of recurrence following standard trastuzumab-based therapy.

Although pERC acknowledged that patients value additional treatment options, the Committee was not satisfied that the addition of neratinib after adjuvant trastuzumab-based therapy addresses the key outcomes that patients have indicated they value, such as reducing the risk of disease recurrence, maintenance of quality of life (although it does offer a convenient, oral treatment), and minimal side effects.

pERC could not draw a conclusion on the cost-effectiveness of extended adjuvant treatment with neratinib due to a lack of confidence in the cost-

	effectiveness estimates obtained, as there was substantial uncertainty surrounding the incremental benefits used in the economic model.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC noted that future trials of adjuvant breast cancer therapy should be adequately designed to detect a difference in treatment effect in the patient population requested for reimbursement. pERC acknowledged that the ExteNET trial is currently ongoing and the final analysis of OS data, which is event driven, could form the basis of a resubmission to pCODR.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Approximately 26,000 new cases of breast cancer, and 5,000 deaths from breast cancer occur each year in Canada. Of the new cases, approximately 95% are early-stage disease (stage I, II, or III), while 5% present with clinically detectable metastatic disease (stage IV). 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. Patients with HER2-positive and HR-positive breast cancer are typically treated with adjuvant or neoadjuvant chemotherapy with trastuzumab-based treatment for one year with the addition of hormone therapy such as tamoxifen or an aromatase inhibitor, bone-targeted drugs, and radiation therapy as needed. 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. pERC agreed that there is a need for more effective therapies for patients at higher risk of recurrence following standard trastuzumab therapy.

pERC deliberated on the results of one randomized, placebo-controlled, phase III trial (ExteNET), 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. pERC noted the drug reimbursement request is for a specific subgroup of patients in the ExteNET trial: HR-positive patients who completed trastuzumab-based therapy within the last year. In this target subgroup, two- and five-year analyses of IDFS showed a clinical benefit in favour of neratinib-treated patients with absolute differences in IDFS at two and five years of 4.5% and 5.1%, respectively. In comparison, pERC noted that the corresponding absolute difference in IDFS between the treatment groups in the overall trial population at two and five years was 2.3% and 2.5%, respectively. pERC discussed that there was a very high-level of uncertainty around the magnitude of the IDFS benefit considering that the subgroup analysis was not pre-specified in the trial protocol and it was a post-hoc exploratory analysis of the ExteNET trial data. pERC commented that the analysis should be considered hypothesis-generating as it was neither appropriately powered to test for treatment effect differences between groups nor was it controlled for multiple testing. As highlighted by the Clinical Guidance Panel (CGP), none of the pre-specified subgroups assessed in the trial demonstrated a statistically significantly different relative benefit from neratinib on interaction testing, suggesting there was no difference in treatment effect within the categories of the subgroups assessed. Therefore, like the CGP, pERC also questioned the biologic rationale for the sponsor's claim of greater efficacy of neratinib in the specific subgroup of patients comprising the funding request. pERC discussed the protocol amendments that occurred during the trial and agreed that the consequences of these amendments (changes to eligibility criteria, decreased sample size, losses to patient follow-up) added to the uncertainty in determining the magnitude of clinical benefit of neratinib compared with placebo. pERC acknowledged that data on OS are currently immature and therefore are unavailable to confirm or refute the IDFS results. The pill burden of neratinib was also discussed and pERC questioned whether the treatment effect may be diminished if treatment adherence is lower in real-world practice than in the ExteNET trial. Considering the multiple sources of uncertainty associated with the evidence, pERC agreed it was not possible to draw a definitive conclusion on the clinical benefit of neratinib as extended adjuvant treatment in patients with early-stage HER2-positive, HR-positive breast cancer who completed trastuzumab-based therapy within the last year. pERC agreed with the CGP's assessment that the results of the post-hoc subgroup analysis require validation in a trial focused to patients at higher risk of recurrence following standard trastuzumab-based therapy.

During reconsideration of the pERC Initial Recommendation, pERC discussed the feedback received from the sponsor and patient advocacy groups that asserted that pERC misinterpreted the subgroup analysis results of the patient group that comprise the reimbursement request; mischaracterized protocol amendments and their impact on the trial results; and was incorrect in suggesting data on OS are required to confirm the clinical benefit of neratinib. In the ExteNET trial, HR status (positive versus negative) and time from completion of trastuzumab (12 months or fewer versus more than 12 months) were individually

pre-specified as subgroups of interest in the trial protocol. However, the specific subgroup that was used to define the requested reimbursement patient population (i.e., HR positive and completed trastuzumab therapy in 12 months or fewer) was in fact not pre-specified and performed as a post-hoc exploratory analysis. As pointed out by the pCODR CGP and Methods Team, the risk of a false-positive result is a valid concern given the number of analyses that were performed in the trial without adjustment for multiple comparison testing. Regarding protocol amendments, pERC agreed with the CGP and the registered clinicians providing feedback that the potential exists for amendments to have influenced the trial results. Amendments nine and 13 resulted in a 25% loss of patients from the intent-to-treat (ITT) patient population and 4.3% fewer patients in the neratinib group (compared with placebo) available for analysis of the primary outcome (IDFS), which is not an insignificant discrepancy considering the low IDFS event rate in the trial (9.8% at five years). pERC agrees with the CGP's assessment that the amendments highlight an overall limitation in the ExteNET trial design to not originally restrict enrolment to a high-risk group of patients with HER2-positive breast cancer most likely to benefit from extended adjuvant treatment. pERC also disagrees with the sponsor's suggestion that OS data are not required to confirm the IDFS benefit associated with neratinib given that IDFS is an accepted surrogate for OS in the adjuvant setting. As noted by the CGP, when trials demonstrate a nominal IDFS benefit, as was observed for neratinib in the ExteNET trial, OS data should be required to confirm clinical benefit. Finally, to address stakeholder comments that referred to the approval of neratinib by Health Canada and reimbursement of neratinib by the National Institute for Health and Care Excellence (NICE), pERC wanted to remind stakeholders that as an independent health technology assessment (HTA) body, pERC's decisions on drug reimbursement should not be influenced by the decisions of other agencies. pERC noted that regulatory agencies have different objectives than HTA bodies. Regulatory agencies generally focus on the minimum efficacy level and acceptable safety profile, while the purpose of HTA is broader in that it examines the comparative effectiveness of different treatment strategies that also takes into consideration other dimensions (e.g., ethical, social) to attain a balance between the values, needs, preferences, and perspectives of patients and the health care system.

pERC deliberated on the safety profile of neratinib and acknowledged that, overall, patients treated with neratinib in the ExteNET trial experienced greater toxicity compared with patients treated with placebo. Gastrointestinal toxicity (GI), diarrhea in particular, was significantly greater in the neratinib group of the ExteNET trial and required dose adjustments/delays and treatment discontinuation in a significant proportion of patients. pERC noted, however, that GI toxicity and its impact on health-related quality of life (HRQoL) appeared to last a few months after initiating neratinib and agreed with the CGP that it is mostly manageable with dose reductions and supportive medications including prophylactic antidiarrheal drugs (e.g., loperamide as assessed in the CONTROL trial). pERC noted that both measurements of HRQoL (Functional Assessment of Cancer Therapy - Breast [FACT-B] and EuroQoL-5D [EQ-5D] scales) demonstrated an initial decrease in scores in both treatment groups at month 3 of neratinib treatment, with scores gradually increasing close to baseline values by month 12, and the minimal clinically important difference (MCID) threshold for each measure was not reached at any time point. However, in reviewing the HRQoL data pERC also considered the CGP's assessment that it was unclear if the results observed in the trial were due to a waning effect, treatment of the toxicity, or also the effect of patients withdrawing from treatment.

During deliberations, pERC considered the patient advocacy group input received that indicated breast cancer patients value having access to effective treatment options that reduce the risk of recurrence, maintain HRQoL, and have minimal side effects. pERC acknowledged neratinib is the only treatment option available as extended adjuvant treatment; however, given the uncertainty associated with the evidence submitted, pERC was unsure whether neratinib adequately addresses the outcomes considered important to patients including reducing the risk of recurrence, maintenance of HRQoL, and minimal side effects. pERC acknowledged that the patient input indicated patients value that neratinib is an oral treatment and are willing to accept the pill burden associated with neratinib treatment.

During reconsideration of the pERC Initial Recommendation, pERC discussed the patient advocacy group feedback received that emphasized the lack of an approved treatment for breast cancer patients at high risk of recurrence following treatment with trastuzumab. pERC acknowledged the need for treatment options for these patients but reiterated that the limitations of the submitted evidence make it unclear if neratinib provides meaningful clinical benefit in this context with respect to the outcomes considered important to patients.

Overall, based on the evidence for the subgroup of patients in the ExteNET trial with HER2-positive, HR-positive breast cancer who completed trastuzumab-based therapy within the last year, pERC concluded it

was not satisfied that there is a meaningful net clinical benefit to the use of extended adjuvant treatment with neratinib in this subgroup of patients. In reaching this conclusion pERC could not ignore the high level of uncertainty around the magnitude of the IDFS benefit given the treatment effect was estimated based on a subgroup analysis that was not pre-specified and exploratory in nature, as well as the limitations of the trial related to protocol amendments, and the lack of OS data to confirm clinical benefit. While pERC acknowledged that neratinib has a significant but manageable toxicity profile, they agreed it is currently unclear whether neratinib prevents disease recurrence in high-risk patients after standard trastuzumab-based therapy with minimal side effects and maintenance of HRQoL.

pERC deliberated on the cost-effectiveness of neratinib compared with no treatment in adult patients with HER2-positive, HR-positive breast cancer who completed prior adjuvant trastuzumab-based therapy in the last year and noted that the pCODR Economic Guidance Panel's (EGP) estimates were higher than the sponsor's base-case estimates. pERC agreed with the EGP's assessment that the duration of the treatment effect and the parametric model selected for extrapolation of IDFS overestimated the benefit of neratinib. pERC discussed that the majority of the incremental benefit (~98%) occurred in the period after the five-year trial duration while the majority of incremental costs (~80%) were accrued within the first year of treatment. Despite making changes to the submitted model in reanalyses to obtain more conservative estimates of the incremental cost-utility ratio (ICUR), the EGP concluded there remains substantial uncertainty surrounding their cost-effectiveness estimates as the majority of the incremental benefit for neratinib occurs in the extrapolation period; therefore, the EGP ICUR is likely underestimated. In light of this uncertainty, and the additional uncertainty around the magnitude of the IDFS benefit, the lack of OS data, and the other limitations of the evidence, pERC stated they did not have confidence in the estimates presented and therefore could not draw a conclusion on the cost-effectiveness of neratinib as extended adjuvant treatment compared with no treatment in patients with HER2-positive, HR-positive breast cancer who completed before adjuvant trastuzumab-based therapy in the last year. pERC indicated that mature OS data from the ExteNET trial would be helpful in addressing the uncertainty in the economic evaluation of neratinib.

pERC discussed the factors that could impact the feasibility of implementing a positive reimbursement recommendation for neratinib and noted that neratinib is expected to be an additional therapy in the adjuvant treatment of patients with HER2-positive, HR-positive early breast cancer. Given that neratinib will not replace other therapies, overall treatment costs would increase if the drug were funded. The EGP noted that the main limitation of the submitted budget impact analysis (BIA) was uncertainty in the derivation of the patient population given the uncertainty with the estimates used. The EGP performed exploratory analyses to assess the impact of a variety of other parameters that were associated with uncertainty and not assessed by the sponsor; according to these analyses, influential parameters on the submitted incremental three-year budget impact included an increase in the proportion of patients with public coverage, which increased the budget impact by approximately 29% if it was increased from 58% to 75%; and changes in dose intensity (from 88% to 100%) and treatment duration (from 10.7 months to 12 months), which increased the budget impact by approximately 14% and 13%, respectively. pERC concluded that the reanalyses performed highlight the uncertainty associated with the submitted BIA, and the submitted budget impact may be underestimated given the prevalence of HER2-positive, HR-positive breast cancer.

During reconsideration of the pERC Initial Recommendation, patient advocacy group feedback indicated disagreement with pERC's assessment that neratinib would be an additional therapy in the adjuvant setting. In response, pERC wanted to clarify that pERC's assessment of neratinib being an additional therapy was in reference to the fact that neratinib would not replace any currently available adjuvant treatment.

EVIDENCE IN BRIEF

The CADTH pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and BIA
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy group(s); the Canadian Breast Cancer Network (CBCN) and the Canadian Organization for Rare Disorders (CORD)
- input from registered clinicians (one joint submission on behalf of three oncologists from Cancer Care Ontario [CCO]; and one single submission from a clinician in Ontario)
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- two patient advocacy groups, CBCN and CORD
- one joint clinician group, CCO
- PAG
- the sponsor, Knight Therapeutics Inc.

The pERC Initial Recommendation was to not recommend reimbursement of neratinib for the treatment of patients with HER2-positive, HR-positive breast cancer who have completed trastuzumab-based therapy within the past 12 months. Feedback on the pERC Initial Recommendation indicated that registered clinicians and the PAG agreed with the Initial Recommendation, while the sponsor and both patient advocacy groups disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR Review Scope

The purpose of the review is 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 12 months.

Studies Included: One randomized, double-blind, placebo-controlled phase III trial

The pCODR systematic review included one randomized, placebo-controlled, phase III trial: ExteNET. ExteNET assessed the efficacy and safety of 12 months of neratinib following trastuzumab-based adjuvant therapy in patients with early-stage HER2-positive breast cancer.
Eligible patients were women ≥ 18 years of age (≥ 20 in Japan) who had confirmed invasive stage I to III HER2-positive breast cancer (later amended to stage II to III) without evidence of recurrence, known HR status, completed neoadjuvant or adjuvant trastuzumab-based therapy up to two years before randomization (later amended to one year), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The trial excluded patients who achieved a pathologic complete response (pCR) or ductal carcinoma in situ (DCIS) and axillary pCR following neoadjuvant therapy; and patients who received prior HER2-directed therapy other than trastuzumab. Patients were centrally randomized to receive oral neratinib 240 mg (6 x 40 mg tablets/day) or matching placebo daily for up to 12 months (or until disease recurrence or toxicity requiring discontinuation) in a 1:1 ratio; and were stratified by HR status, nodal status, and trastuzumab adjuvant regimen (sequentially versus concurrently with chemotherapy). Dose reductions to 200 mg, 160 mg, and 120 mg daily were permitted for the management of toxicity.

The trial consisted of three parts: a primary analysis period of 2 years (part A), an extended follow-up of three to five years (part B), and long-term follow-up of OS (part C). The trial protocol had multiple amendments resulting from 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 to III, node positive, who completed trastuzumab less than or equal to one year before randomization), reducing the required sample size, with primary analysis to be performed in this enriched population (termed as amended ITT or aITT population). A later amendment stopped further recruitment of patients and truncated the follow-up duration from five years to two years, further reducing the required sample size.

The final protocol amendment restored the original primary analysis (i.e., two-year IDFS in the ITT population which included both low and high-risk patients) and follow-up was restored to five years (or longer for OS), which required patients to re-consent to extended follow-up. Notably, data from years three to five were collected retrospectively, with fewer patients available due to loss to follow-up.

A total of 2,840 patients were randomized and constituted the ITT population. At the end of the two-year primary analysis period, a total of 53 patients died and therefore were not available for extended follow-up. Of the remaining 2,787 patients, 2,117 patients (76%) re-consented to the five-year extended follow-up.

The reimbursement request is for a subgroup of the ExteNET trial population consisting of 1,334 HR-positive patients who completed trastuzumab-based therapy within the last year. This target subgroup was not pre-specified in the trial protocol/statistical analysis plan and was analyzed post hoc; therefore, results of this analysis are exploratory and descriptive.

A total of 2,816 patients received at least one dose of the study drug, for a median treatment duration of approximately 11 months. More than 75% of patients in the neratinib group received at least 80% of the planned 240 mg/day dose during the treatment period.

The pCODR review also provided contextual information on the CONTROL trial; an ongoing open-label, phase II trial assessing the incidence and severity of diarrhea in patients with early-stage HER2-positive breast cancer treated with neratinib and intensive loperamide prophylaxis. All three antidiarrheal prophylaxis regimens assessed in the CONTROL trial (loperamide alone or in combination with budesonide or colestipol) appeared to reduce diarrheal episodes, duration and severity, and neratinib dose modification due to diarrhea compared with the neratinib group in the ExteNET trial. The incidence and severity of diarrhea over the course of neratinib treatment was also markedly reduced.

Patient Populations: Median age of 52 years; majority of patients were stage II to III (71.6%), HR positive (57.4%), and node positive (76.4%)

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. At baseline, the median age of trial patients (N = 2,840) was 52.3 years, 53.3% of patients were post-menopausal, 71.6% had stage II to III tumours, 47.3% had poorly differentiated histology, and 94% had ductal carcinoma. More than half of trial patients were HR-positive (57.4%). In terms of nodal status, 46.8% had 1 to 3 positive nodes and 29.6% had ≥ 4 positive nodes, while 23.6% were node negative. A majority of patients received concurrent trastuzumab and chemotherapy before randomization (62.3%); the median time from diagnosis to randomization was 22.05 months; and the median time from last treatment with trastuzumab to randomization was 4.50 months. The majority of patients had trastuzumab less than or equal to one year from randomization (80.9%) and patients received adjuvant trastuzumab for a median of 11.43 months. A total of 721 (25.4%) patients received prior neoadjuvant therapy; among these 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.

Patients who re-consented for part B of the trial and those in the target patient subgroup of interest (HR-positive patients and completed trastuzumab within the past year; N = 1,334) had a similar distribution of baseline characteristics compared with the ITT patient population and treatment groups were well-balanced in all characteristics.

Key efficacy results: Modest difference in IDFS in favour of neratinib; post-hoc exploratory subgroup analysis

The primary efficacy outcome of the ExteNET trial was IDFS at two years, defined as the time from randomization to the first occurrence of any one of the following events: invasive ipsilateral breast tumour recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause. This definition differs from the standardized efficacy end points (STEEP) system in adjuvant breast cancer trials as it excludes second non-breast primary events. Secondary outcomes included disease–free survival (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 OS. HRQoL was an exploratory end point, measured using the Functional Assessment of Cancer Therapy - Breast (FACT-B) and EuroQoL-5D (EQ-5D) scales. All end points were analyzed at two years and five years, with the exception of HRQoL, which was analyzed at 12 months.

The final analysis of OS is planned to be performed after 248 deaths are observed. With the exception of OS, none of the other secondary outcomes or subgroup analyses, including the target subgroup, were controlled for multiplicity.

Patient-reported Outcomes: No clinically meaningful differences in HRQoL at 12 months

Patient-reported outcomes were reported for the ITT patient population. A total of 2,407 patients (84.8%) completed FACT-B questionnaires at least once post-baseline, and the questionnaire completion rates were balanced between treatment groups at all timepoints; questionnaire completion rates were approximately 80% or more until month nine, after which the completion rate was lower (approximately 70%). Overall, FACT-B scores decreased in both treatment groups during treatment; the most pronounced difference between groups occurred at month one 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 HRQoL is consistent with the GI adverse events (AEs) (specifically diarrhea) reported during the first few months following neratinib treatment. At month three 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 (7 to 8 points) was not reached in either group at any time point for either the total or individual scale scores of FACT-B.

A total of 2,427 patients (85.5%) completed at least one EQ-5D measurement post-baseline, and the questionnaire completion rates were balanced between treatment groups at all timepoints. 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 (visual analogue scale [VAS] and index) in both treatment groups. The mean EQ-5D VAS scores decreased from baseline at month 1 by 2.3 points in the placebo group and 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 (0.09 to 0.10 and 7 to 10 units for the EQ-5D index and VAS scores, respectively) was not reached for either score at any assessment time point. The initial decrease in HRQoL as reported by the EQ-5D is consistent with the GI AEs (specifically diarrhea) reported during the first few months following neratinib treatment.

Safety: Neratinib associated with greater toxicity overall, and diarrhea

Safety outcomes were reported for the ITT patient population. Overall, more patients in the neratinib group experienced AEs (98.5% versus 88.1%), grade ≥ 3 AEs (49.7% versus 13.1%), serious AEs (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 to 3) was the most frequently reported AE among neratinib-treated patients compared with placebo (95.3% versus 35.4%); diarrhea led to neratinib dose reductions in 372 (26%) patients versus 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. Patients in the neratinib group also reported more grade 1 to 2 fatigue (25% versus 2%), vomiting (23% versus 8%), abdominal pain (22% versus 10%) and upper abdominal pain (14% versus 7%), rash (15% versus 7%), decreased appetite (12% versus 3%), and muscle spasms (11% versus 3%). Incidences of serious AEs were low (7.3% in the neratinib group versus 6.0% in the placebo group), and in the neratinib group were mostly GI or hepatic in nature.

Need and Burden of Illness: Effective therapies for patients at high-risk of recurrence

Patients with HER2-positive and HR-positive breast cancer are typically treated with adjuvant or neoadjuvant chemotherapy with trastuzumab-based treatment for one year with the addition of hormone therapy such as tamoxifen or an aromatase inhibitor, bone-targeted drugs, and radiation therapy as needed. Although the vast majority of cancers do not relapse, there are several hundreds of patients per year who die of metastatic HER2-positive HR-positive breast cancer in Canada. According to the CGP, metastatic HER2-positive breast cancer is considered a lethal condition. Improving outcomes of patients at high-risk of recurrence following standard trastuzumab therapy has been the subject of several recent publications, including this trial (ExteNET), the adjuvant pertuzumab trial (APHINITY), and the trastuzumab emtansine trial (KATHERINE).

Registered Clinician Input: Neratinib best offered to higher risk patients; benefits of trastuzumab emtansine more clinically meaningful in this setting with less toxicity

Two registered clinician inputs (one joint and one individual) were provided for this submission. All clinicians highlighted the unmet need for treatment options for patients with early breast cancer, and the need to improve clinical outcomes. It was also noted there are currently no other treatment options in the extended adjuvant treatment setting for patients with early breast cancer after adjuvant trastuzumab. The single clinician input identified the treatment burden associated with neratinib and highlighted that as patients will have already completed chemotherapy and one year of trastuzumab, neratinib may not be strongly recommended or accepted given the additional impact related to monitoring, toxicities, and side effects management. It was noted that the absolute benefit for the overall population of early breast cancer patients was low; and clinicians from both inputs were in agreement that preference would be to use neratinib for patients with a higher risk of relapse where a greater absolute benefit would be expected, including those who are node positive (especially N2) and have large tumours (T3 or T4). The registered clinicians providing input also stated a preference for the use of trastuzumab emtansine following neoadjuvant treatment over extended adjuvant treatment with neratinib, as they viewed the results of the KATHARINE trial as more clinically meaningful and the side effect profile of trastuzumab emtansine as more favourable. There were differing opinions among the clinician inputs regarding the generalizability of neratinib to other subgroup populations (stage I, node negative, small tumours, completed trastuzumab therapy within the last two years, completed neoadjuvant/adjuvant pertuzumab plus trastuzumab).

PATIENT-BASED VALUES

Values of Patients with HER2-positive early breast cancer: reduce risk of recurrence, maintenance of HRQoL, and minimal side effects

Two patient advocacy groups provided input on neratinib for HER2-positive breast cancer in patients who completed adjuvant trastuzumab-based therapy: CBCN and CORD. Both inputs highlighted the negative physical and emotional impact of a breast cancer diagnosis and treatment. Patient respondents from CBCN noted that treatments cause significant impact on lives of patients, not only due to the disruption of going to treatments but also due to the many side effects that they experience as a result of treatment. Patient respondents had experience with a variety of current treatments (surgery, chemotherapy, hormone therapy, targeted therapy, radiation) and described them effective overall with side effects that included cardiac toxicity, fever, fatigue, diarrhea, muscle and joint pain, and nausea. Tolerability of side effects varied; some patients described them as manageable, while others found the side effects challenging or were left with lasting effects (neuropathy). Quality of life was also affected by current therapies; patients cited side effects including fatigue, inability to work and financial burden, and some found it inconvenient to access treatment. Patients indicated they most valued a reduced risk of recurrence, maintenance of quality of life, and minimal side effects when choosing a treatment option. Among five patients interviewed who had experience with neratinib, all reported experiencing side effects either immediately upon starting neratinib or up to two weeks after the first dose. The most common side effect was diarrhea, reported as severe to very severe by four out of the five patients. Loperamide was prescribed to four patients as prophylaxis before starting neratinib and while on therapy; and these patients reported it reduced the severity and frequency of diarrhea but did not totally resolve diarrheal incidents until two to four months into treatment. Other side effects reported included vomiting, fever, stomach aches, headaches, and liver toxicity. CORD noted that patients who received neratinib were willing to tolerate a great deal to increase the likelihood of living without cancer recurrence or metastasis, even if the increase was slight. The side effects clearly outweighed the challenges of therapy.

ECONOMIC EVALUATION

Economic Model Submitted: Cost-utility and cost-effectiveness analyses

The EGP assessed the cost-utility (clinical effects measured as quality-adjusted life-years [QALYs] gained) and cost-effectiveness (clinical effects measured as life-years gained) of neratinib compared with no treatment in adult patients with HER2-positive, HR-positive breast cancer who are less than one year from the completion of prior adjuvant trastuzumab-based therapy.

Basis of the Economic Model: Clinical and economic inputs

The submitted Markov model was comprised of five health states: IDFS, local recurrence, remission, distant recurrence and death. The economic evaluation was based on clinical efficacy (IDFS) and AE data (five-year datacut) from a subgroup of patients from the ExteNET trial that align with the patient population in the funding reimbursement request. Utility data were sourced from the ExteNET trial and other international publications that included breast cancer patients as well as healthy patients.

The costs considered in the economic evaluation included those for drugs and drug administration, medical resource use pre- and post-recurrence, and AEs.

Drug Costs: Treatment for one year

At the submitted price, neratinib costs $45.00 per 40 mg tablet. At the recommended dose of 240 mg (six 40 mg tablets) given orally once daily, neratinib costs $270.00 per day, $7,560.00 per 28-day course and $98,550.00 for one year.

Cost-effectiveness estimates: Substantial uncertainty in cost-effectiveness estimates

The sponsor's best estimate (probabilistic) of the ICUR was $46,936 per QALY over a 55-year (lifetime) time horizon. The EGP noted that the submitted cost-effectiveness estimates of neratinib were driven by the extrapolated results beyond the five-year trial period with less than 3% of the incremental benefits accrued over the trial duration and the majority of incremental costs (80%) accrued within the first year. The submitted analysis was based on a five-year datacut (sensitivity analysis) that had limitations (retrospective data collection; losses to patient follow-up). The EGP requested the sponsor provide an analysis using the two-year datacut (primary efficacy analysis) to validate the base-case analysis results. The sponsor provided an abridged version of the model incorporating the two-year data, however, this model version was not flexible to allow testing of alternate assumptions and the results did not align with the five-year analysis results, appearing to overestimate the long-term incremental benefit of neratinib based on the extrapolation approach used. The EGP therefore did not undertake any reanalyses based on the two-year datacut and performed reanalyses based on the five-year datacut. The EGP reanalyses were based on the following factors:

- *Duration of treatment effect of neratinib was overestimated:* The sponsor assumed that the treatment effect of neratinib was maintained after the trial period (12 years for neratinib and 16 years for no treatment). The CGP suggested this duration of treatment benefit was overestimated. The EGP applied a tapering of effect that shortened the treatment effect to 10 years, which was considered by the CGP to be more appropriate and similar to the follow-up period in the HERA trial.
- *Model fit for IDFS was uncertain and likely overestimates the benefit of neratinib:* The sponsor used a flexible spline-based (1-knot) Weibull distribution for extrapolation of IDFS, which the EGP considered an overestimated incremental hazard ratio over time for neratinib compared with BSC. The EGP selected a better-fitting parametric distribution, the stratified general gamma distribution, which they considered more appropriate based on visual fit and criteria for model selection, the trajectory of patients based on the two-year and five-year data analyses, and also considering the CGP's reservations regarding the internal validity of the clinical results (protocol amendments; post-hoc subgroup analysis) and the lack of mature OS data. As over 98% of the incremental benefit occurs in the period after the five-year trial duration, the extrapolation assumption is a key factor in assessing the cost-effectiveness of neratinib.
- *Utility values likely overestimate the benefit of neratinib:* The sponsor's utility value sources and values were associated with uncertainty and not well justified. The EGP applied utility values in line with the sponsor's scenario analysis that used the same data source for all base health states.
- *Proportion of patients receiving treatment in the metastatic setting:* Based on the sponsor's own clinical expert input, as well as input from the CGP, the submitted model overestimated the proportion of patients who would receive metastatic treatment. The EGP conducted reanalyses based on alternate values provided by the CGP that were considered more representative of Canadian clinical practice.
- *Resource use in the post-recurrence setting:* The CGP considered the sponsor's assumptions regarding the use of different treatments in the post-recurrence setting as inaccurate. The EGP conducted reanalyses based on the alternate values provided by the CGP.

The EGP concluded that the sponsor's submitted economic evaluation underestimates the ICUR for the comparison of neratinib versus no treatment. The EGP's reanalysis resulted in an ICUR best estimate (probabilistic) of $82,326 per QALY, which is higher than the sponsor's base-case estimate. The key drivers of the incremental benefit were the duration and magnitude of the treatment effect; and the main cost drivers were the acquisition cost of neratinib and cost to treat recurrence. As the majority of the incremental benefit for neratinib occurs in the extrapolation period, the EGP concluded there is substantial uncertainty surrounding their cost-effectiveness estimate. The EGP further noted that concerns with the ExteNET trial data (protocol amendments; post-hoc subgroup analysis) introduce additional uncertainty into the economic evaluation and therefore the ICUR presented by the EGP is likely underestimated.

ADOPTION FEASIBILITY

Considerations for Implementation and Budget Impact: Additional resources required; budget impact is uncertain and may be underestimated

PAG identified the following factors that could impact the implementation of neratinib: the large pill burden (six tablets per day) may make adherence to treatment difficult for patients, especially for those taking other oral medications; and additional resources (nursing, pharmacy, and clinic visits) will be required as neratinib would be an additional therapy in a large patient population, which currently is being monitored/observed. Specifically, PAG identified supportive management (e.g., antidiarrheal prophylaxis such as loperamide), monitoring and management of adverse effects (i.e., drug interactions with CYP3A4 inhibitors, grade 3 or 4 diarrhea/nausea, and hepatotoxicity), and long-term monitoring for cardiac toxicity would all be required. The oral route of administration of neratinib was considered an enabler to implementation; however, PAG noted that in some jurisdictions oral medications are not funded in the same mechanism as intravenous cancer medications; in this case, patients would first have to file an application to their pharmacare program, which may limit accessibility of treatment for patients and cause financial burden on patients and their families in the form of co-payments and deductibles. PAG commented that the other coverage options in those jurisdictions that fund oral and intravenous cancer medications differently are private insurance or full out-of-pocket expenses. PAG also noted that the one tablet strength of 40 mg would allow for dose adjustments and there would be minimal drug wastage.

The sponsor provided a Canada-wide BIA to assess the feasibility of implementing a reimbursement recommendation for neratinib as extended adjuvant treatment in patients with HER2-positive, HR-positive breast cancer who are less than one year from the completion of prior adjuvant trastuzumab-based therapy. The factors found to influence the BIA the most included the drug acquisition cost of neratinib, the duration of treatment with neratinib and dose intensity, the size of the eligible population, and the market share. Increases in each of these assumptions from baseline increased the budget impact of neratinib. The main limitation of the BIA model was uncertainty in the derivation of the patient population given the uncertainty with the estimates used. The EGP performed exploratory analyses to assess the impact of a variety of parameters that were associated with uncertainty and not assessed by the sponsor, including duration of treatment, dose intensity, changes to the proportions of patients with distant versus local recurrences, changes to the proportions of patients with invasive disease over three years, and the proportion of patients with public coverage. According to the EGP's reanalyses, the submitted incremental three-year budget impact increased by approximately 29% if public coverage increased from 58% to 75%; it increased by 14% if dose intensity was increased from 88% to 100%; and increased by 13% if treatment duration increased from 10.7 months to 12 months.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Matthew Cheung, who was absent from the meeting
- Dr. Maureen Trudeau, who was excluded from chairing and voting due to a conflict of interest
- Dr. Anil Abraham Joy, who was excluded from voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Maureen Trudeau, who was excluded from chairing and voting due to a conflict of interest
- Dr. Anil Abraham Joy, who was excluded from voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of neratinib for early breast cancer, through their declarations, two members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, were excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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