CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pertuzumab and Trastuzumab for Early Breast Cancer

November 29, 2018

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

List of Abbreviations

AEs	Adverse events
AIs	Aromatase inhibitors
CGP	Clinical Guidance panel
CI	Confidence interval
CR	Complete response
DFS	Disease-free survival
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQOL 5 Dimensions Questionnaire
EMA	European Medicines Agency
HR	Hazard ratio
HER2	Human epidermal growth factor receptor 2
HRQOL	Health-related quality of life
HT	Hormone therapy
IDFS	Invasive disease-free survival
INV	Investigator assessment
IRC	Independent review committee
ITT	Intent-to-treat
MCID	Minimal clinically important difference
MEDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
pCR	Pathological complete response
pERC	pCODR Expert Review Committee
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RCT	Randomized controlled trial
RT	Radiotherapy
QLQ-C30 and BR23	Quality of Life Questionnaire Core-30 and breast-specific module
RCTs	Randomized controlled trials
RECIST	Response Evaluation Criteria for Solid Tumours
SAEs	Serious adverse events
SAP	Statistical analysis plan
SD	Standard deviation
SERMs	Selective estrogen receptor modulators

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 pertuzumab and trastuzumab for the adjuvant treatment of early 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 pertuzumab and trastuzumab for the adjuvant treatment of early 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; 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. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on pertuzumab and trastuzumab for the adjuvant treatment of early breast cancer, a summary of submitted Provincial Advisory Group Input on pertuzumab and trastuzumab for the adjuvant treatment of early breast cancer, and a summary of submitted Registered Clinician Input on pertuzumab and trastuzumab for the adjuvant treatment of early breast cancer, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of pertuzumab in combination with trastuzumab (Perjeta and Herceptin) compared with placebo and trastuzumab, both combined with chemotherapy, as adjuvant treatment (after surgery) in patients with HER2-positive early stage breast cancer.

Pertuzumab (Perjeta) is a recombinant humanized monoclonal antibody and is a first-in-class HER2 dimerization inhibitor. It inhibits the dimerization of HER2 with other HER receptors, which prevents them from signalling in ways that promote cell growth and proliferation. Pertuzumab has a Health Canada indication that reflects the requested patient population for reimbursement. Pertuzumab in combination with trastuzumab and chemotherapy has been issues marketing authorization for the adjuvant treatment of patients with HER2-positive early breast cancer with lymph node positive and/or hormone receptor negative disease.

The Health Canada recommended dose of pertuzumab is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over a period of 30 to 60 minutes. An observation period of 30 to 60 minutes is recommended after completion of each PERJETA infusion. The observation period should be completed prior to any subsequent dose of HERCEPTIN or chemotherapy.

PERJETA and HERCEPTIN should be administered sequentially and can be given in any order. When administered with PERJETA, the recommendation is to follow a 3-weekly schedule for HERCEPTIN administered as an IV infusion with an initial loading dose of 8 mg/kg followed every 3 weeks thereafter by a dose of 6 mg/kg body weight.

In patients receiving a taxane, PERJETA and HERCEPTIN should be administered prior to the taxane. When administered with PERJETA, the recommended initial dose of docetaxel is 75 mg/m^2.

In patients receiving an anthracycline-based regimen, PERJETA and HERCEPTIN should be administered following completion of the anthracycline treatment.

In the adjuvant setting (after surgery), PERJETA should be administered in combination with HERCEPTIN for a total of one year (maximum 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first), as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy. PERJETA and HERCEPTIN should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One RCT, APHINITY,[1] was identified that met the eligibility criteria of the pCODR systematic review. A summary of the trial and key outcomes are presented below.

APHINITY

APHINITY is an ongoing, international, multi-centre, phase 3, double-blind, placebo-controlled RCT comparing the efficacy and safety of pertuzumab-trastuzumab versus placebo-trastuzumab, both combined with chemotherapy, as adjuvant treatment after surgery for patients with HER2-positive early stage breast cancer.

The trial enrolled patients from 549 centres in 43 countries including Canada (23 sites; n=110).[2] Just over half of trial patients (approximately 53%) were from centres in Canada, Western Europe, Australia/New Zealand, and South Africa. The trial was funded and designed, in consultation with the trial investigators, by the Sponsor, Hoffman La Roche/Genentech. The Sponsor also had an active role in trial conduct including data collection and analysis, and manuscript preparation.

Patients included in APHINITY met the following key criteria:

- Age ≥ 18 years
- Newly diagnosed, non-metastatic, adequately excised (total mastectomy or breast conserving surgery), histologically confirmed invasive HER2-positive breast cancer
- HR status known
- Node-positive (pN ≥1; any tumour size except T0) or node-negative (pN0; any tumour diameter >1 cm)
- Node-negative tumours between 0.5 and 1 cm were also eligible if at least one of the following high-risk factors were present:
    - Histologic or nuclear grade 3
    - Estrogen and progesterone HR negative
    - Age < 35 years
- ECOG performance status of 0-1
- Patients treated previously with chemotherapy (including therapy administered in the neoadjuvant setting), radiotherapy, anti-HER2 therapy, or immunotherapy were excluded.

The primary outcome of the trial was invasive DFS (IDFS), a composite endpoint, defined as the time from randomization until the date of the first occurrence of one of the following invasive disease events: recurrence of ipsilateral invasive tumour, recurrence of ipsilateral locoregional invasive disease, distant recurrence, contralateral invasive breast cancer, or death from any cause. The secondary outcomes of the trial included IDFS (STEEP definition), DFS (includes second primary invasive non-breast cancers and non-

invasive breast cancer), OS, relapse-free interval, and distant relapse-free interval. Patient-reported HRQOL was considered an exploratory outcome of the trial.

Patients were randomized to pertuzumab-trastuzumab or placebo-trastuzumab using centralized randomization that was stratified by nodal status, adjuvant chemotherapy, HR status, and geographic region. A trial protocol amendment (protocol version B, dated November 20, 2012) resulted in the exclusion of further node-negative patients into the trial, an increase in sample size (from 3806 to 4800 patients) that included only node-positive patients, and the addition of protocol version as a stratification factor. The required number of IDFS events and power of the trial did not change as a result of the amendment; 379 events were still required to provide 80% power to detect an HR of 0.75 at a 5%, two-sided, significance level. A three-year IDFS rate of 89.2% was expected in the placebo group versus an assumed three-year IDFS rate of 91.8% (based on data from the BCIRG 006 trial) in the pertuzumab group, which corresponds to an absolute three-year difference in IDFS of 2.6% between the treatment groups.

Key secondary outcomes of the trial (IDFS by STEEP, DFS and OS) were tested if the primary analysis of IDFS demonstrated superiority (statistical significance) of pertuzumab-trastuzumab over placebo-trastuzumab. The other secondary endpoints (relapse-free interval and distant relapse-free interval) were tested but not included in the adjustment for multiple testing, and therefore should be considered exploratory endpoints. The trial was also powered to compare OS between the treatment groups; three interim analyses and a final analysis of OS are planned (adjusted for multiplicity), with the first to occur at the time of the primary analysis and the final to occur when 640 deaths have occurred, which is approximately nine to 10 years after the last patient was randomized. Subgroup analyses of the primary outcome were performed by stratification, patient and disease-related factors.

A total of 4805 patients were randomized to receive chemotherapy and trastuzumab plus either pertuzumab (n=2400) or placebo (n=2405). Patients received either pertuzumab or placebo (840 mg intravenously as a loading dose, followed by 420 mg intravenously every three weeks) combined with trastuzumab (8 mg intravenously per kg of body weight as a loading dose, followed by 6 mg per kg every three weeks), beginning at the first cycle of taxane chemotherapy and continuing for a maximum of 18 treatment cycles (one year). Choice of permitted adjuvant chemotherapy (6 to 8 cycles) was at the discretion of investigators and could be anthracycline or non-anthracycline-based. Dose modifications were not permitted for either targeted agent, however, dose delays/interruptions were allowed. At the time of the primary analysis, 84.5% of patients in the pertuzumab-trastuzumab group and 87.4% of patients in the placebo-trastuzumab group had completed study treatment. The median duration of study treatment (chemotherapy and targeted therapy) and targeted therapy were the same in both groups at 64 weeks and 55 weeks, respectively.

Overall, the baseline characteristics of patients were well balanced between the two treatment groups. Most patients were treated at trial sites in the geographic categories of Canada/Western Europe/Australia/New Zealand/South Africa (54%) and Asia-Pacific (23%).[3] The median age of patients was 51 years, with 13% of patients aged 65 and older. All patients had centrally confirmed HER2-positive tumours and an ECOG performance status of 0 or 1. The majority of patients had HR-positive (64%) and node-positive disease (63%)[3]. Of the 37% (n=1799) of patients with node-negative disease, 3.6% (n=174) and 33.8% (n=1625) had tumour sizes of ≤1 cm and >1cm, respectively. When the entire trial population is considered, approximately 6% of patients had tumours <1 cm in size.[4] The trial enrolled 11(<1%) male patients. Most patients in the trial were randomized into the trial under protocol version A (76%).

The primary analysis population is comprised of 4804 patients, and not the 4805 patients originally randomized; one patient in the placebo-trastuzumab group was excluded after randomization on the basis of falsification of personal information.[3] The key efficacy and safety outcomes of the APHINITY trial are summarized in Table 1.

Efficacy

The primary analysis is based on a data cut-off date of December 19th, 2016, at which time the median follow-up of patients in the trial was 45.4 months (3.78 years):

- APHINITY met its primary outcome demonstrating a statistically significant improvement in IDFS in the pertuzumab treatment group (HR=0.81, 95% CI, 0.66-1.00; p=0.045). The three-year rates of IDFS were 94.1% in the pertuzumab group and 93.2% in the placebo group (absolute difference of 0.9%). Distant recurrences were the most frequent first invasive disease-free event to occur in both treatment groups; 4.7% (n=112) in the pertuzumab group and 5.8% (n=139) in the placebo group; and these distant metastases were in the CNS in approximately 1.9% and 1.8% of patients, respectively.
- Most subgroup analyses demonstrated a treatment effect that favoured treatment with pertuzumab-trastuzumab, with the exception of patients with node-negative disease (HR=1.13, 95% CI, 0.68-1.86), which favoured treatment with placebo. The greatest magnitude of treatment benefit with pertuzumab was observed in patients who were post-menopausal (HR=0.68, 95% CI, 0.51-0.91), had node-positive disease (HR=0.77, 95% CI, 0.62-0.96), and tumour size less than 2 cm (HR=0.62, 95% CI, 0.42-0.92); however, tests for interaction for these subgroups (and all other subgroup analyses but one) were non-significant, suggesting the treatment effect was not significantly different among the categories of patients in each subgroup examined.
- Since a statistically significant result was obtained for the primary outcome, the secondary outcomes of the trial were tested sequentially in the following order: IDFS (STEEP), DFS, and OS.
    - The alternate definitions of DFS evaluated in the trial were consistent with the primary outcome results. IDFS by STEEP definition, which includes second primary invasive non-breast cancers (HR=0.82, 95% CI, 0.68-0.99; p=0.043), and DFS, which includes second primary invasive non-breast cancers and non-invasive breast cancers (HR=0.81, 95% CI, 0.67-0.98; p=0.033), produced treatment effect estimates of similar magnitude to the primary outcome definition of IDFS.
- At the primary analysis cut-off date, a total of 169 patients had died; 80 (3.3%) in the pertuzumab-trastuzumab group and 89 (3.7%) in the placebo-trastuzumab group. The first interim analysis of OS data did not demonstrate a significant difference in mortality between the treatment groups (HR=0.89; 95% CI, 0.66-1.21; p=0.47). The OS data are currently immature with an information fraction of 26%.[3]

HRQOL[5]

Patient-reported HRQOL was assessed in the trial using the EORTC QLQ-C30, EORTC QLQ breast-specific module (BR23), and EQ-5D questionnaires.

Patients in both treatment groups reported a clinically meaningful decline in mean QLQ—C30 global health status scores from baseline to the end of taxane chemotherapy (−11.2 [95% CI, −12.2 to −10.2] and −10.2 [95% CI, −11.1 to −9.2] in the pertuzumab and placebo

groups, respectively), with scores returning to baseline during targeted treatment. No clinically significant difference in mean scores was observed between the groups.

In terms of patient functioning, mean scores in physical, cognitive, role, social, and emotional functioning scales were comparable between the treatment groups over time, and no clinically meaningful declines in mean scores were observed between the treatment groups for any scale except for physical functioning. Physical functioning scores declined from baseline until the end of taxane chemotherapy but returned to baseline during targeted therapy. Mean physical function scores were -10.7 (95% CI, -11.4 to -10.0) and -10.6 (-11.4 to -9.9) in the pertuzumab and placebo groups, respectively.

In terms of symptoms, the scales for fatigue, dyspnea, and appetite loss all showed clinically meaningful worsening in mean scores from baseline to the end of taxane chemotherapy in both treatment groups; however, no clinically meaningful differences in mean scores between groups were observed. Patients in both treatment groups reported worsening in diarrhea symptoms over time that persisted until the end of taxane chemotherapy; the mean change in score from baseline was 29.8 (95% CI, 21.0 to 23.6)[5] in the pertuzumab group and 9.2 (95% CI, 8.2 to 10.2) in the placebo group. While scores in both groups improved over time they remained elevated during targeted treatment, and the deterioration was clinically meaningful in the pertuzumab group but not in the placebo group. Other symptom scores, including financial difficulties, insomnia, nausea/vomiting, constipation, and pain showed no clinically meaningful changes in mean scores from baseline during the trial.

For the EORTC QLQ-BR23, no clinically meaningful differences in mean scores from baseline were observed between the treatment groups for body image, systemic chemotherapy side effects, arm symptoms, breast symptoms, and future perspectives. Approximately 300 patients in each treatment group reported hair loss and sexual activity. In these patients a clinically meaningful deterioration in hair loss scores was observed in both treatment groups from baseline to the end of taxane chemotherapy, which persisted during targeted therapy. A decline in sexual enjoyment scores was considered clinically meaningful in both treatment groups at the end of taxane chemotherapy, which persisted during targeted therapy in the pertuzumab group only.

No major differences (≥ 5 percentage points) were seen between the treatment groups in the five EQ-5D domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[3]

Safety

The most common all-grade treatment-emergent AEs (pertuzumab versus placebo) observed in the APHINITY trial included diarrhea (71.2% versus 45.2%), nausea (69% versus 65.5%), alopecia (66.7% versus 66.9%), fatigue (48.8% versus 44.3%), vomiting (32.5% versus 30.5%), arthralgia (28.7% versus 32.5%), and constipation (28.9% versus 31.6%);[3] with the largest differences between treatment groups found for diarrhea and rash (25.8% versus 20.3%).

The incidence of grade ≥3 AEs were higher in the pertuzumab group at 64.2% compared to 57.3% in the placebo group. The higher incidence in the pertuzumab group was mainly driven by diarrhea (9.8% versus 3.7% with placebo). The frequency of grade ≥3 diarrhea was higher in patients treated with pertuzumab combined with non-anthracycline chemotherapy (18%) compared to anthracycline chemotherapy (7.5%). After cessation of chemotherapy, the incidence of grade ≥3 diarrhea was 0.5% in the pertuzumab group and 0.2% in the placebo group. Other grade ≥3 AEs (pertuzumab versus placebo) included

neutropenia (16.3% versus 15.7%), febrile neutropenia (12.1% versus 11.1%), anemia (6.9% versus 4.7%), and neutrophil count decreased (9.6% in both groups).

SAEs were slightly higher in the pertuzumab-trastuzumab treatment group compared to placebo (29.3% versus 24.3%), which were primarily attributable to febrile neutropenia (8.8% versus 8.1%), diarrhea (2.5% versus 0.7%), and infections/infestations (6.8% versus 3.3%).[3]

Treatment delay/interruption and discontinuation of one or more study drugs (including chemotherapy) due to AEs were slightly higher with pertuzumab-trastuzumab therapy compared to placebo-trastuzumab (delay/interruption, 51.5% versus 44.2%; discontinuation, 13.1% versus 11.5%). Dose delay/interruption and discontinuation of pertuzumab/chemotherapy were also higher with pertuzumab-trastuzumab therapy compared to placebo-trastuzumab (delay/interruption, 30.6% versus 26.3%; discontinuation, 7.0% versus 5.8%). [3] The most common AEs that lead to pertuzumab treatment discontinuations were ejection fraction declines, cardiac failure and diarrhea.[3]

The incidence of fatal AEs (deaths) were 0.8% in both the pertuzumab (n=18) and placebo (n=20) treatment groups.

Cardiac Events of Special Interest

Primary cardiac events occurred in twice as many patients treated with the combination of pertuzumab-trastuzumab (0.7%, n=17) compared to placebo-trastuzumab (0.3%; n=8); Of these patients, 0.6% (n=15) and 0.2% (n=6) met the criteria for NYHA class III or IV heart failure with LVEF decline, respectively, and two patients in each group (0.1%) died from cardiac causes. In the pertuzumab group, 15 of the 17 primary cardiac events occurred in patients treated with anthracycline chemotherapy. Secondary cardiac events (asymptomatic or mildly symptomatic NYHA class II substantial LVEF decline) occurred in 2.7% (n=64) of patients in the pertuzumab group and 2.8% (n=67) of patients in the placebo group.

Limitations

Critical appraisal of the APHINITY trial was based on the primary trial publication, additional data published in posters presented at ASCO 2018, and unpublished data provided to pCODR by the Manufacturer. Overall, the trial was of good quality. The randomization procedure was carried out appropriately although details of allocation concealment were not reported. The treatment groups were well balanced at baseline for important patient and prognostic characteristics, and length of time on treatment was the same in both treatment groups. There was also transparent reporting of the disposition of patients through the trial; reasons for treatment and follow-up discontinuation were balanced between the treatment groups, and all efficacy analyses were performed according to the ITT principle. Notwithstanding the quality of the trial, a number of limitations were noted, and areas of uncertainty identified, which are important when interpreting the results of the APHINITY trial, and include the following:

- Protocol amendment B, which stopped the enrolment of further node-negative patients into the trial (thereby increasing the proportion of node-positive patients into the trial) and increased the sample by approximately 1000 patients, changed the composition of patients in the trial, and as a result, there is a possibility that APHINITY may not be entirely representative of all patients with HER2-positive breast cancer. It is also unclear how the sample size increase affected the power of the trial. It is possible that the trial may have been overpowered, as it detected an absolute difference in IDFS at three years between the groups that was smaller

(0.9%) than what was specified as the clinically important difference in the amended SAP (2.6%). Larger sample size is associated with increased statistical power; as sample size and power increase, progressively smaller differences between treatment groups in the primary outcome will be identified as statistically significant.[7] However, differences between treatment groups identified as statistically significant may not be clinically significant. The clinical significance of the treatment benefit observed with pertuzumab combination treatment in APHINITY is questionable.

- At the primary analysis, the APHINITY trial demonstrated a statistically significant difference in IDFS in favour of pertuzumab-trastuzumab. The stratified HR in the ITT population was 0.81 (0.66-1.00; p=0.045), suggesting a 19% reduction in the risk of invasive disease events (absolute difference of 0.9% in IDFS at three years). However, the upper confidence limit was the null value of 1.00, which indicates there is insufficient evidence to conclude that the groups were indeed statistically significantly different.

  Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter suggesting that it is incorrect to refer to the observed statistical difference as being "marginal," as the reported p-value was less than 0.05 (and the upper limit of the confidence interval for the hazard ratio (HR) was exactly 0.995). pERC discussed the response provided by the pCODR Methods Lead in the pCODR Clinical Guidance Report and agreed the difference was statistically significant. Furthermore, pERC noted that the results of the primary analysis are cited as they appear in the primary trial publication (HR for IDFS = 0.81; 95% CI, 0.66 to 1.00; P = 0.045); therefore, no change is required in the style used for reporting of the confidence interval.

- The Submitter's Health Canada indication and pCODR funding request is focused on patients with HER2-positive breast cancer at high-risk of recurrence, which they have defined by the presence of either node-positive disease or HR-negative disease. The evidence informing this request is from subgroup analysis results of the trial. The pCODR Methods Team disagrees with the Submitter that the evidence from these analyses clearly demonstrate treatment with pertuzumab is more efficacious in these particular patients; specifically:

  - The subgroups analyses were pre-specified but exploratory, and therefore not desinged to test for differences in treatment effect among categories of patient subgroups. The analyses were also not adjusted for multiplicity (type 1 error); 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 APHINITY trial numerous analyses (secondary, subgroup, and sensitivity) were performed.

  - The treatment effect estimate obtained for the node-positive patient subgroup was HR=0.77 (95% CI, 0.62-0.96), and for the HR-negative subgroup was HR=0.76 (95% CI, 0.56-1.04); the absolute difference between groups in three-year IDFS was 1.8% and 1.6%, respectively. Upon closer examination of the events in the HR-negative subgroup, it appears the trend observed in this subgroup is likely driven by the high proportion of node-positive patients in this group.[6] The treatment effect size obtained for another patient subgroup, tumour size <2 cm (HR=0.62; 95% CI, 0.42-0.92), was actually of greater magnitude than that observed for node-positive patients, but this patient group was not discussed in the Submitter's definition of high-risk of recurrence. It seems reasonable that

tumour size would be of similar prognostic importance as nodal or HR status. The Submitter's rationale for selecting patients at high-risk for recurrence (HR-negative status and not tumour size) is unclear to the pCODR Methods Team; and does not align with the subgroup analysis results of the trial.

  - The statistical tests for interaction were non-significant for all but one subgroup analysis (menopausal status), which suggests that all patient factors examined, including nodal and HR status, were not associated with a statistically significant difference in treatment effect. Therefore, there is little evidence of heterogeneity of treatment effect between the patient subgroups.
  - The efficacy of pertuzumab in node-negative patients should be considered unclear based on the APHINITY trial data. The amendment change that reduced the number of these patients in the trial and the low event rate (n=32 in the pertuzumab group versus n=29 in placebo group) precludes any conclusions on efficacy.

- Ten pre-specified sensitivity analyses were performed to assess the robustness of the primary outcome results; results from half (five) of these analyses did not align with the primary analysis results (were not statistically significant).[3]

  In their feedback on the initial recommendation, the submitter disagreed with pERC's statement that the Committee is not satisfied that there is a clinically meaningful net clinical benefit of pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy. Specifically the submitter argued that:

  (1) There is a clinically meaningful net clinical benefit of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive early breast cancer at high risk of recurrence. APHINITY was the largest international, multi-centre, phase III double-blind, placebo-controlled randomised study conducted of pertuzumab + trastuzumab + chemotherapy as adjuvant treatment in almost 5,000 HER2-positive early breast cancer patients. This study's primary analysis was the first to improve upon the high bar set by the current standard of care in this curative setting and to demonstrate statistically significant superiority in IDFS over placebo + trastuzumab + chemotherapy in the intention-to-treat population (ITT) (IDFS HR = 0.813; 95% CI, 0.664 to 0.995; P = 0.0446; two-sided alpha = 5%).

  In response to the submitter's feedback the pCODR Methods lead reiterated that a protocol amendment increased the sample size of the APHINITY trial by approximately 1000 patients. While it is unclear how this significant increase in sample size affected the power of the trial, it is quite possible that APHINITY was overpowered, as it detected an absolute difference in IDFS between treatment groups at three years of 0.9%, which is smaller than the 2.6% difference that was pre-specified as clinically significant in the SAP. The Methods Team maintains that the clinical significance of the 0.9% absolute difference in IDFS between the treatment groups in the APHINITY trial remains questionable.

  (2) There is a clinically meaningful net clinical benefit of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive early breast cancer node-positive disease. In a situation where the ITT analysis is positive, it is appropriate to investigate the consistency of the

primary analysis results across pre-specified subgroups. In early breast cancer, including HER2-positive breast cancer, lymph node involvement is associated with poor prognosis. Patients in this pre-defined subgroup derived even greater benefit from the addition of pertuzumab with an IDFS hazard ratio estimate that was lower than in the overall ITT population. On average, patients in this large lymph node positive subgroup (N=3,005) derived a 23% reduction in the risk of recurrence or death (IDFS HR = 0.768; 95% CI, 0.616 to 0.958).

In response to the submitter's feedback the pCODR Methods lead agreed that in trials where the ITT analysis for the primary outcome is statistically significant, it is appropriate to investigate the consistency of the results in pre-specified subgroups of patients. However, it should be acknowledged that in most trials, including APHINITY, subgroup analyses are exploratory in nature, and therefore should be considered hypothesis-generating since they are not designed to test for differences in treatment effect among categories of patients within a subgroup. Further, the subgroup analyses in APHINITY were not controlled for multiple testing (which increases the risk of type 1 error; claiming a difference when one does not truly exist), and tests for statistical interaction were non-significant for every subgroup examined with the exception of menopausal status, which provides little evidence of heterogeneity of treatment effect. Therefore, based on the identified limitations and the results obtained, the Methods Team maintains that the subgroup analyses do not clearly demonstrate that the combination of pertuzumab-trastuzumab is more efficacious in lymph node positive patients.

- HRQOL was an exploratory endpoint of the APHINITY trial, and as such, the results of the QOL assessment should be interpreted as descriptive. Caution is advised in making inferences based on the reported treatment comparisons considering that, for most QOL scales, it was not indicated whether mean scores in the treatment groups were similar at baseline. The QOL data are further limited by selective reporting; numerical or descriptive data (graphs or figures) were not presented for a number of QLQ-C30 scales (cognitive, social and emotional functioning; majority of symptom scales) and for all BR23 scales.

Table 1: Key efficacy and safety outcomes in the APHINITY trial.[1]

Outcomes	Trastuzumab + Pertuzumab (n=2400)	Trastuzumab + Placebo (n=2404)
Data cut-off date	December 19, 2016	
Median follow-up, months	45.4	
Primary outcome		
Invasive DFS[a]		
No. events (%)	171 (7.1)	210 (8.7)
Category of first invasive DFS event:[b]		
Distant recurrence	112 (4.7)	139 (5.8)
CNS metastases	45 (1.9)	44 (1.8)
Locoregional recurrence	26 (1.1)	34 (1.4)
Contralateral breast cancer	5 (0.2)	11 (0.5)
Death without previous event	28 (1.2)	26 (1.1)
3-year event-free rate, %	94.1	93.2
Hazard ratio (95% CI); p-value	0.81 (0.66-1.00); p=0.045	
Secondary outcomes		
Invasive DFS - STEEP Definition[c]		
No. events (%)	189 (7.9)	230 (9.6)
3-year event-free rate, %	93.5	92.5
Hazard ratio (95% CI); p-value	0.82 (0.68-0.99); p=0.043	
DFS[d]		
No. of events (%)	192 (8.0)	236 (9.8)
3-year event-free rate, %	93.4	92.3
Hazard ratio (95% CI); p-value	0.81 (0.67-0.98); p=0.033	
Relapse-free interval[e]		
No. of events (%)	138 (5.8)	173 (7.2)
3-year event-free rate, %	95.2	94.3
Hazard ratio (95% CI); p-value	0.79 (0.63-0.99); p=0.043	
Distant relapse-free interval[f]		
No. of events (%)	119 (5.0)	145 (6.0)
3-year event-free rate, %	95.7	95.1
Hazard ratio (95% CI); p-value	0.82 (0.64-1.04); p=0.101	
OS		
No. of events (%)	80 (3.3)	89 (3.7)
Hazard ratio (95% CI); p-value	0.89 (0.66-1.21); p=0.47	
Safety, %	n=2364	n=2405
AEs (any grade)	99.9	99.5
Grade ≥3	64.2	57.3
SAEs	29.3	24.3
AEs leading to treatment discontinuation	13.1	11.5
Fatal AEs	0.8	0.8

Abbreviations: AEs - adverse events; CI confidence interval; CNS - central nervous system; DFS - disease-free survival; OS - overall survival; SAEs - serious adverse events.

Notes:
[a] - Invasive DFS is a composite endpoint and was defined as the time from randomization until the date of the first occurrence of one of the following events: ipsilateral invasive breast tumour recurrence, recurrence of ipsilateral locoregional invasive disease, a distant recurrence, contralateral invasive breast cancer, or death from any cause. This definition excludes second primary non-breast cancer as an invasive disease event.
[b] - Patients who had an additional invasive-disease event within 61 days of their first event are reported in the category according to the following hierarchy: distance recurrence, locoregional recurrence, contralateral breast cancer, and death without a previous event.
[c] - Invasive DFS - STEEP Definition - is defined the same way as the primary outcome of invasive DFS but

the STEEP definition includes second primary non-breast cancers (with the exception of non-melanoma skin cancers and in situ carcinoma of any site).
[d] - DFS was defined as the time between randomization and the date of first occurrence of an invasive disease-free survival event including a second primary non-breast cancer event or contralateral or ipsilateral DCIS.
[e] - Relapse-free interval was defined as the time between randomization and the date of local, regional or distant breast cancer recurrence.
[f] - Distance relapse-free interval was defined as the time between randomization and the date of distant breast cancer recurrence.
*Hazard ratios < 1.00 favour treatment with pertuzumab.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, the diagnosis of HER2-positive breast cancer, as well as the treatments used, could impact both the emotional and physical well-being. CBCN noted that most patients currently receive a combination of the anti-HER2 therapy, trastuzumab, in addition to standard chemotherapy. CBCN reported that some of the side effects of HER2 positive breast cancer and the therapies used to manage this disease include: cardiac toxicity, fever, cough, muscle pain, fatigue, diarrhea and nausea. Many of these symptoms have the ability to impact daily life, primarily: fatigue, pain and nausea. According to CBCN, the financial burden associated with living with breast cancer extends far beyond any loss of income during a temporary or permanent absence from employment. In addition to the loss of income during illness, breast cancer patients can incur substantial costs associated with treatment and disease management

According to CBCN it is important for patients to have access to therapies that will extend their life expectancy without significantly increasing side effects that will negatively impact their daily lives. Also, as HER2-positive breast cancers are shown to be at higher risk of recurrence than HER2 negative tumours, the goal of therapy is to target cancer cells in the body and reduce the risk of disease recurrence. According to CBCN the following factors were shown to affect patients' choice of treatment options (in order of importance): effectiveness of the treatment, reducing the risk of recurrence, maintaining quality of life and maintaining mobility, maintain productivity, minimal side effects, minimal medical appointments and ability to continue childcare duties.

In total, two patient respondents indicated having experience with the pertuzumab and trastuzumab combination. Respondent noted that it was difficult for them to determine if the side effects experienced were form the chemotherapy or from the combination therapy. One patient experienced mild nausea, taste changes, fatigue, low white blood cell count and mouth cankers, but ranked her quality of life as medium and tolerable. The other patient experienced nausea, chills, diarrhea, and hunger, and chose to suspend her treatment (after approximately one month of treatment) but maintains that her quality of life always resumed, as she never had more than two days in bad health. Relative to the experienced side effects, participants had an overall positive attitude towards the combination treatment, reporting gratitude at having access to this treatment and expressed that more women should have access to this treatment.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarity on eligible patient population
- Use of the combination post-surgery in patients who have received a few cycles of trastuzumab with chemotherapy in the neoadjuvant setting before surgery

Economic factors:

- Drug wastage for trastuzumab (more likely in small centres where vial sharing is minimal)
- Reimbursement of only the combination package of pertuzumab and trastuzumab, rather than the single agent pertuzumab vial

Registered Clinician Input

Two clinician inputs were provided one from an individual oncologist and one group input.

This treatment is indicated for HER2-positive early breast cancer patients at high risk of recurrence, defined as either node-positive or hormone receptor-negative disease. In terms of the clinical benefit, it was noted in the joint input that the improvement demonstrated in the node-positive patients was minimal in the APHINITY trial and that there was no real advantage in node-negative patients. While the clinicians acknowledged the benefit of pertuzumab and trastuzumab, when compared with placebo and trastuzumab for invasive disease-free survival in the APHINITY trial, they were unsure if the observed benefit is clinically meaningful given the lack of a significant difference in overall survival. In addition, the clinicians providing the joint input did not believe this treatment fills an unmet need because there are effective treatments available already, and the trial only demonstrated a modest improvement. It was noted by the individual clinician providing input that overall the trial results in the adjuvant setting were disappointing, however, selective use of this therapy could benefit higher risk populations including node positive patients. For clinical use, pertuzumab would be added in combination with trastuzumab and not sequentially. Companion diagnostic testing would include HER2 positive testing, which is already done as routine standard of practice.

Summary of Supplemental Questions

There were no supplemental questions identified for this review

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and 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 pertuzumab and trastuzumab for the adjuvant treatment of early breast cancer.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the APHINITY Trial[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>High-risk of recurrence after surgery</td><td>
• The trial enrolled patients with newly diagnosed, non-metastatic, adequately excised, HER2-positive early stage (1-3) breast cancer at high-risk of recurrence
• High-risk was defined in the trial as either node-positive or HR-negative disease
<table>
<tr><th>Nodal and HR status</th><th>Pertuzumab N (%)</th><th>Placebo N (%)</th></tr>
<tr><td>Node-positive</td><td>1503 (62.6)</td><td>1502 (62.5)</td></tr>
<tr><td>Node-negative</td><td>897 (37.4)</td><td>902 (37.5)</td></tr>
<tr><td>HR-positive</td><td>1536 (64.0)</td><td>1546 (64.3)</td></tr>
<tr><td>HR-negative</td><td>864 (36.0)</td><td>858 (35.7)</td></tr>
</table>
• Pre-specified but exploratory analyses of IDFS by patient nodal status and HR status were performed:
<table>
<tr><th>Nodal and HR status</th><th>HR (95% CI) for pertuzumab vs. placebo</th></tr>
<tr><td>Node-positive</td><td>0.77 (0.62-0.96)</td></tr>
<tr><td>Node-negative</td><td>1.13 (0.68-1.86)</td></tr>
<tr><td>HR-positive</td><td>0.86 (0.66-1.13)</td></tr>
<tr><td>HR-negative</td><td>0.76 (0.56-1.04)</td></tr>
</table>
• Tests for interaction of the treatment effect were non-significant for all nodal and HR patient subgroups.
</td><td>Is the Submitter's definition of high risk of recurrence after surgery generalizable to the Canadian practice?</td><td>The definition of high risk HER2 positive breast cancer is controversial, but may include patients with node positive disease, and/or hormone receptor negative tumours. Clinically, node positive disease has been traditionally considered at higher risk for disease recurrence in the Canadian population, due to the higher stage of disease (i.e. tumour burden) at presentation. The impact of hormone receptor negative tumours in the context of HER2 positive status remains less clear, as the main driver of risk in this population is considered to be HER2 overexpression. As more genomic information about the biology of HER2 positive breast cancer becomes available, this may also help better stratify patients into high/low risk groups.</td></tr>
<tr><td></td><td>Small tumors less than 1 cm.</td><td>
Nodal status
• Patients with node-negative and node-positive tumours < 1.0 cm were limited to <10% of the total number of randomized patients.
• Patients with HR-negative and HR-positive tumours < 1.0 cm were limited to <10% of the total number of randomized patients.
</td><td>Do the trial results apply to patients with node negative disease and tumours ≤1.0cm? If so, why?</td><td>The CGP does not support generalizing the study results to hormone receptor negative HER2-positive breast cancers less than 1 cm in size. It has not been established that these tumours are considered high risk, and data from APHINITY did not support pertuzumab in this subgroup.</td></tr>
</table>

Domain	Factor	Evidence from the APHINITY Trial[1]	Generalizability Question	CGP Assessment of Generalizability
				However, the CGP supports generalizing the study results to node-positive HER2 positive breast cancers less than 1 cm in size, as the driver of risk in these patients is node positive disease, not so much the primary tumour size.
	Inflammatory breast cancer	Patients with inflammatory breast cancer were excluded from the trial.	Do the trial results apply to patients with Inflammatory breast cancer? If so, why?	While the adjuvant trial did not include patients with inflammatory (i.e. locally advanced) HER2 positive breast cancer, there is biological rationale to suggest that treatment benefits in the node positive patient population would be generalization to this patient group.
	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.)?	As patients with an ECOG performance status of 2 or greater were excluded from both neoadjuvant and adjuvant pertuzumab trials, there is no data to support the generalizability of treatment benefit in this patient population.
	Serious cardiac illness or medical condition	Patients with serious cardiac illness or medical conditions including but not confined to history of documented heart failure or systolic dysfunction (LVEF <50%) were excluded from the trial.	Do the trial results apply to patients with serious cardiac illness/conditions? If so, why?	Patients with serious cardiac illness/conditions were excluded from pertuzumab trials, and results cannot be generalized to this population.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the APHINITY Trial[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Age</td><td>
• The trial enrolled patients aged ≥ 18 years. The age distributions of patients were as follows:
<table>
<tr><th>Age group</th><th>Pertuzumab N (%)</th><th>Placebo N (%)</th></tr>
<tr><td>< 40 years</td><td>326 (13.6)</td><td>327 (13.6)</td></tr>
<tr><td>40-49 years</td><td>708 (29.5)</td><td>702 (29.2)</td></tr>
<tr><td>50-65 years</td><td>1051 (43.8)</td><td>1082 (45.0)</td></tr>
<tr><td>≥ 65 years</td><td>315 (13.1)</td><td>293 (12.2)</td></tr>
</table>
• Pre-specified but exploratory analyses of invasive DFS by age group were performed:
<table>
<tr><th>Age group</th><th>HR (95% CI) for pertuzumab vs. placebo</th></tr>
<tr><td>< 40 years</td><td>0.96 (0.59-1.59)</td></tr>
<tr><td>40-49 years</td><td>0.89 (0.60-1.32)</td></tr>
<tr><td>50-64 years</td><td>0.78 (0.57-1.07)</td></tr>
<tr><td>≥ 65 years</td><td>0.70 (0.41-1.17)</td></tr>
</table>
• Tests for interaction of the treatment effect were non-significant for all age groups.
</td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>As there were no statistical associations between age groups and treatment effect, overall trial results can be generalized to all age groups included in the trial (>18 years of age).</td></tr>
<tr><td></td><td>Male Sex</td><td>The trial included 11 (<1%) male patients.</td><td></td><td>Results should be generalized to male breast cancer patients given the biologic rationale and the common practice to extrapolate breast cancer results to male patients.</td></tr>
<tr><td></td><td>Organ dysfunction</td><td>The trial excluded patients that did not meet pre-specified criteria regarding organ function.</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Efficacy or safety of pertuzumab was not studied in patients excluded from trial participation due to organ dysfunction. Therefore, we cannot generalize treatment benefits to these patient populations.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the APHINITY Trial[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Ethnicity or Demographics</td><td>The race of enrolled patients was as follows:<table><tr><th>Race</th><th>Pertuzumab %</th><th>Placebo %</th></tr><tr><td>White</td><td>71.2</td><td>70.5</td></tr><tr><td>Asian</td><td>24.7</td><td>24.9</td></tr><tr><td>Other</td><td>4.1</td><td>4.6</td></tr></table></td><td>If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.</td><td>The demographics of trial participants is similar to the overall Canadian population. Therefore, the CGP is comfortable generalizing these results to the Canadian population.</td></tr>
<tr><td>Intervention</td><td>Treatment Intent</td><td>The treatment intent in the trial was curative.</td><td>Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)</td><td>Separate published trials (i.e. CLEOPATRA)[8] have confirmed significant survival benefit in the metastatic setting. Therefore, therapeutic benefit of Pertuzumab has been demonstrated in both the curative and palliative treatment settings.</td></tr>
<tr><td></td><td>Line of therapy</td><td>• The APHINITY trial assessed pertuzumab-trastuzumab in the adjuvant setting.
• APHINITY trial eligibility criteria required that patient have non-metastatic operable primary invasive carcinoma of the breast that is histologically confirmed and adequately excised. Patients must have undergone either a total mastectomy or breast conserving surgery.
• The trial did not include patients who received any systemic chemotherapy (e.g., neoadjuvant) or radiotherapy before surgery.</td><td>Are the results of the trial generalizable to other lines of therapy (e.g. neo-adjuvant?)</td><td>In 2015, pCODR[9] reviewed the use of pertuzumab in combination with trastuzumab in the neoadjuvant setting and concluded that there was insufficient evidence to support a claim of net clinical benefit for this combination for patients with early operable, locally advanced, or inflammatory breast cancer. This was based on review of the NeoSphere trial[10], which used pathologic complete response (pCR) as a primary endpoint. Although pCR is associated with improved survival among specific breast cancer subtypes, response to</td></tr>
</table>

Domain	Factor	Evidence from the APHINITY Trial[1]	Generalizability Question	CGP Assessment of Generalizability
				neoadjuvant chemotherapy is not a validated surrogate endpoint for disease-free or overall survival in breast cancer (Cortazar 2014[11]). Unfortunately, the neoadjuvant trials were underpowered. We will likely not get sufficiently powered trials to evaluate survival in this setting. The CGP accepts the assertion that evidence of net clinical benefit in patient with node positive disease is generalizable to patients who would start the 18 cycles of treatment in the neoadjuvant setting (i.e., before surgery) and continue treatment up to the maximum dose of 18 cycles after surgery.
	Number of treatment cycles	Patients in the trial were treated for a maximum of 18 cycles (1 loading dose and 17 maintenance doses) within 1 year. The median number of cycles of pertuzumab received by patients was 18 (range, 1-22).	Are the results of the trial generalizable to other numbers of treatment cycles?	18 cycles, in combination with trastuzumab is considered the standard treatment therapy. Therefore, benefit from alternative treatment regimens cannot be generalized to the Canadian patient population.
Outcomes	Appropriateness of Primary and Secondary Outcomes	• Primary outcome: Invasive DFS (modified STEEP definition, which excludes second primary invasive non-breast cancers) • Secondary outcome: Invasive DFS (STEEP, includes second primary invasive non-breast cancers)	Were the primary and secondary outcomes appropriate for the trial design?	We acknowledge that the use of a modified invasive DFS endpoint limits interpretation of the treatment benefit, by providing a more conservative estimate of effect. However, in the absence of mature overall survival data, the CGP accepts this endpoint for decision making, and the results are therefore generalizable to Canadian clinical practice.
	Assessment of Key Outcomes	Are the key outcomes assessed differently in the trial compared with clinical practice in Canada?	If the trial used a different method of assessment than that used in Canadian clinical	The CGP finds no difference in the method of outcome assessment used in the trial population. Therefore, the results of key

Domain	Factor	Evidence from the APHINITY Trial[1]	Generalizability Question	CGP Assessment of Generalizability
			practice, are the results of the trial applicable to the Canadian setting?	outcomes can be generalized to Canadian clinical practice.
Setting	Countries participating in the Trial	The trial was conducted in 549 centres in 43 countries including Canada (n=110)	If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	The Canadian patient population actively participated in this APHINITY clinical trial. The majority of participating countries share similar practice patterns. Therefore, results are generalization to the Canadian breast cancer population.
	Location of the participating centres	The trial was conducted in both academic and community centres.	If the trial was conducted only in academic centres are the results applicable in the community setting?	Both academic and community centres participated in the APHINITY trial. This is similar to Canadian practice patterns. Therefore, the results are generalizable to the Canadian patient population.
	Supportive medications, procedures, or care	Adjuvant hormone and radiation therapy were administered according to standard local practice.	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	Administration of endocrine therapy and radiation therapy are considered standard of care in Canadian practice. Therefore, trial results are generalizable to the Canadian patient population.
Notes: CGP = clinical guidance panel; DFS = disease free survival; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; HER2 = human epidermal growth factor receptor 2; HR-negative = hormone receptor negative; HR-positive = hormone receptor positive; IDFS = invasive disease free survival.				

1.2.4 Interpretation

Burden of Illness and Need

Breast cancer remains one of the most common malignancies affecting Canadian patients, with high rates of both incidence and prevalence.[12] A large proportion of these tumours are HER2 positive, which was traditionally associated with poorer prognosis and more aggressive disease.[13] The diagnosis of breast cancer causes significant stress and anxiety to both patients and their families. This stress is compounded by the negative effects of adjuvant therapy, and worry about future disease recurrence. As a result, more effective and less toxic therapies which improve survival rates are urgently required, and desired by the Canadian population.

The administration of trastuzumab (Herceptin, Roche), an anti-HER2 monoclonal antibody, in combination with adjuvant chemotherapy, has significantly reduced the risk of disease recurrence in HER2 overexpressed breast carcinoma. Recently, pertuzumab (Perjeta, Roche) has been approved for the treatment of metastatic HER2 positive breast cancer[14,15] as well as the management of locally-advanced disease.[16,17] The combination of trastuzumab and pertuzumab has been demonstrated to significantly improve median overall survival in patients with metastatic HER2 positive breast cancer, from 40.8 months (with trastuzumab alone) to 56.5 months (with combination therapy).[15] In the neoadjuvant setting, combination trastuzumab/pertuzumab demonstrated a significant improvement in pathologic complete response rate (pCR) as compared to trastuzumab-based therapy.[16,18] The addition of pertuzumab does not appear to substantially increase the risk of cardiac toxicity, when compared to use of trastuzumab alone.[19] This makes pertuzumab an attractive candidate for use in the adjuvant management of high risk HER2 positive breast cancer.

The definition of high risk HER2 positive breast cancer is controversial, but may include patients with node positive disease, and/or hormone receptor negative tumours. Clinically, node positive disease has been traditionally considered at higher risk for disease recurrence, due to the higher stage of disease (i.e. tumour burden) at presentation. The impact of hormone receptor negative tumours in the context of HER2 positive status remains less clear, as the main biological driver of risk in this population is considered to be HER2 overexpression. As more genomic information about the biology of HER2 positive breast cancer becomes available, this may also help better stratify patients into high/low risk groups. Defining high risk patients who may benefit most from combination therapies is crucial for assessing the clinical utility and cost effectiveness of novel biologic drugs such as pertuzumab.

Effectiveness

One RCT, APHINITY, was identified that met the eligibility criteria of this adjuvant review. APHINITY is a Phase 3, double-blind, placebo-controlled randomized controlled trial with 1:1 randomization ratio.[20] The study enrolled approximately 4804 participants in 43 countries, over a period between November 2011 and August 2013. The Canadian population was well represented, with participation of 23 trial sites and 110 participants. Most randomized patients were treated at trial sites in the geographic categories of Canada/Western Europe/Australia/New Zealand/South Africa (54%) and Asia-Pacific (23%). Details of enrollment criteria are carefully outlined in section 6.3.2. Most importantly, participants required a diagnosis of node-positive disease, or node-negative disease (if tumour diameter >1 cm). Interestingly, the definition of high risk node negative disease in this RCT included tumours between 0.5 and 1cm if they had at least one additional high-risk feature: histologic or nuclear grade 3, estrogen and progesterone HR negative and/or age < 35 years. In clinical practice, the definition of factors that identify high-risk disease

remain under active debate. Participants also required adequate organ function, and a baseline left ventricular ejection fraction of at least 55%.

The primary outcome of the trial was invasive DFS (IDFS), a composite endpoint, defined as the time from randomization until the date of the first occurrence of one of the following invasive disease events: recurrence of ipsilateral invasive tumour, recurrence of ipsilateral loco regional invasive disease, distant recurrence, contralateral invasive breast cancer, or death from any cause. This definition of IDFS is different from the established STEEP definition[21], by excluding second primary invasive non-breast cancers. Both definitions exclude in situ carcinomas, including DCIS and LCIS (non-invasive breast cancers), and non-melanoma skin cancers. According to the submitter, this primary endpoint was chosen to meet FDA requirements. However, the standard STEEP definition of IDFS is often the primary outcome of adjuvant breast cancer trials, as it takes into consideration the difficulty in distinguishing second primary invasive cancers from breast cancer metastases, and the possibility of second malignancies related to treatment. It is important to note that the primary outcome of the trial, IDFS, which is a composite endpoint, has not been validated in the published literature. In addition, it likely provides a more conservative estimate of treatment effect, compared to the other secondary DFS endpoints assessed in the trial (which also include the STEEP definition.[21]

Participants were randomized to either chemotherapy + trastuzumab + pertuzumab, or to chemotherapy + trastuzumab + placebo. Treatment duration was a maximum of 18 cycles within one year in both groups. Importantly, the choice of chemotherapy in the APHINITY trial differed from that studied in the neoadjuvant NeoSphere trial. Specifically, participants in the NeoSphere trial received 4 cycles of neoadjuvant docetaxel, followed by 3 cycles of adjuvant FEC.[16] Participants in the APHINTY trial were treated with various combinations of chemotherapy, including adjuvant FEC or FAC plus either docetaxel or weekly paclitaxel, AC or EC plus either docetaxel or weekly paclitaxel, or with docetaxel/carboplatin.[20] The majority of participants completed the treatment protocol in both study groups (84.5% in the pertuzumab group versus 87.4% in the placebo group).

It is important to note that there was a major protocol amendment which excluded additional node-negative patients into the trial, increased the sample size, and added protocol version as a stratification factor. It is unclear how the sample size increase affected the power of the trial. It is possible that the trial may have been overpowered, as it detected an absolute difference in IDFS at three years between the groups that was smaller (0.9%) than what was specified as the clinically important difference in the amended SAP (2.6%). Larger sample size is associated with increased statistical power, however statistically significant differences may not be clinically significant. The clinical significance of a 0.9% treatment benefit observed with pertuzumab combination treatment in APHINITY is therefore questionable. The APHINITY trial was also powered to compare OS between the treatment groups, however these data remain immature.

Subgroup analyses of the primary outcome were pre-specified, but exploratory and uncontrolled for multiple testing. The most important subgroups that affected interpretation of trial results included nodal status, hormone receptor status, histological grade, and tumour size. Overall, the majority of patients (63%) had node positive disease.

While APHINITY met its primary outcome and crossed the pre-specified statistical boundary for superiority, the upper confidence limit is the null value of 1.00. The HR of IDFS in the overall patient population was 0.81 (95% CI, 0.66-1.00; p=0.045). The three-year rates of IDFS were 94.1% in the pertuzumab group and 93.2% in the placebo group (absolute difference of 0.9%). Interestingly, when the STEEP definition of IDFS was applied, the event rate increased, with a HR of 0.82 95%CI 0.68-0.99 p=0.04). However, the CGP acknowledged that the primary analysis was conducted relatively early with a low number of patients experiencing an event, given that

patients with early breast cancer may relapse after many years. Results may be updated pending subsequent analysis (next analysis due in 2.5 years, and ending at 10 years of follow-up).

The subgroup analyses were pre-specified but exploratory, and therefore not designed to test for differences in treatment effect among categories of patient subgroups. The analyses were also not adjusted for multiplicity, and the chance of a false positive result cannot be discounted. The treatment effect estimate obtained for the node-positive patient subgroup was 0.77 (0.62-0.96), and for the HR-negative subgroup was 0.76 (0.56-1.04); the absolute difference between groups in three-year IDFS was 2.9% and 0.4%, respectively. These estimates suggest the difference in IDFS was statistically significant for node-positive patients but not for HR-negative patients. It appears the trend observed in the HR-negative subgroup is likely driven by the high proportion of node-positive patients in this group. The submitter confirmed that the majority of patients in the HR negative subgroup also had node positive disease, and that a higher percentage of IDFS events happened in those patients who are HR negative and also have node positive disease, versus patients who are HR negative and have node negative disease across both treatment groups.

The treatment effect size obtained for another patient subgroup, tumour size <2 cm (HR=0.62, 95% CI, 0.42-0.92), was actually of greater magnitude than that observed for the node-positive subgroup, but this patient group was not discussed in the submitter's definition of high-risk of recurrence. After reaching out to the submitter, confirmation was received that approximately halve of patients in the subgroup with tumor size <2 cm were lymph-node positive across both treatment groups. Hence there is a possibility that the observed treatment effect in this subgroup is partly driven by the lymph-node positive patients. The submitter's rationale for selecting patients at high-risk for recurrence (HR-negative status and not tumour size) is unclear to the pCODR methods team, and does not align with the subgroup analysis results of the trial.

Safety

Patient-reported HRQOL was considered an exploratory outcome of the trial. HRQOL results were not reported in their entirety (for all scales); therefore the data as presented are selectively reported by the Submitter. However, baseline functional quality of life scores were similar between the treatment groups, and remained stable during treatment, except for a clinically meaningful decrease at the end of taxane treatment.[20]

The incidence of all-grade, treatment emergent AEs was 99.9% in the pertuzumab-trastuzumab group and 99.5% in the placebo-trastuzumab group, and were more apparent during the chemotherapy portion of treatment. The most common all-grade AEs (pertuzumab versus placebo) included diarrhea (71.2% versus 45.2%), nausea (69% versus 65.5%), alopecia (66.7% versus 66.9%), fatigue (48.8% versus 44.3%), vomiting (32.5% versus 30.5%), arthralgia (28.7% versus 32.5%), constipation (28.9% versus 31.6%), with the largest differences between treatment groups found for diarrhea and rash (25.8% versus 20.3%).

The incidence of grade ≥3 AEs were higher in the pertuzumab group at 64.2%, compared to 57.3% in the placebo group, mainly driven by diarrhea (9.8% versus 3.7% with placebo). Overall, patients treated with pertuzumab had an earlier onset of diarrhea, which was worse in grade and longer in duration compared to placebo patients despite intervention with loperamide, which was administered in approximately double the amount of patients (35.6% versus 14.8%). However, after cessation of chemotherapy the incidence of grade ≥3 diarrhea was 0.5% in the pertuzumab group, and 0.2% in the placebo group. This is line with results from the metastatic population.[15]

SAEs were slightly higher in the pertuzumab-trastuzumab treatment group compared to placebo (29.3% versus 24.3%), which were primarily attributable to febrile neutropenia (8.8% versus 8.1%), diarrhea (2.5% versus 0.7%), and infections/infestations (6.8% versus 3.3%).

Treatment interruption/modification and discontinuation due to AEs were slightly higher with pertuzumab-trastuzumab therapy compared to placebo-trastuzumab, for both any treatment (interruption/modification: 51.5% versus 44.2%; discontinuation: 13.1% versus 11.5%) and considering pertuzumab/placebo treatment (interruption/modification: 30.6% versus 26.3%; discontinuation: 7.0% versus 5.8%). The most common AEs that lead to pertuzumab treatment discontinuations were ejection fraction declines, cardiac failure and diarrhea.

It is important to note that while there were differences in AE rates between study groups, absolute rates remained low with no new safety signals detected in the pertuzumab treatment group. There was no difference in incidence of fatal AEs (deaths) between the treatment groups (3.3% in the pertuzumab group vs. 3.7% in the placebo group, HR 0.89, 95%CI 0.66-1.21, p=0.47).

Cardiac Events

Primary cardiac events occurred in twice as many patients treated with the combination of pertuzumab-trastuzumab (0.7%, n=17) compared to placebo-trastuzumab (0.3%; n=8); Of these patients, 0.6% (n=15) and 0.2% (n=6) met the criteria for NYHA class III or IV heart failure with LVEF decline (primary cardiac endpoint of the trial), respectively, and two patients in each group (0.1%) died from cardiac causes. In the pertuzumab group, 15 of the 17 primary cardiac events occurred with patients treated with anthracycline chemotherapy. At the time of the data cut-off date, LVEF recovery was achieved in 53.3% (n=8/15) of patient in the pertuzumab group compared to 66.7% (n=4/6) in the placebo group; median time to LVEF recovery was longer in the pertuzumab-treated patients (27 weeks versus 16.3 weeks in placebo patients). Overall, these absolute numbers remain low and are clinically reasonable in the adjuvant setting, but speak to the need for cardiac monitoring and possible intervention during therapy. In addition, it also appeared that cardiac events in the pertuzumab group were more likely in patients treated with anthracycline therapy, prior to HER2-directed therapy (0.8% vs. 0.4%).

Secondary cardiac events (asymptomatic or mildly symptomatic NYHA class II substantial LVEF decline) occurred in 2.7% (n=64) in the pertuzumab group and 2.8% (n=67) of patients in the placebo group; among these patients, LVEF recovery was achieved in 79.7% and 80.6% of patients, respectively, and median time-to acute recovery was comparable between treatment groups.

PAG Clinical Scenario Questions

Several questions have been raised regarding the applicability of these results to certain clinical scenarios:

1) PAG is seeking clarity on patients who would be eligible for pertuzumab trastuzumab treatment. PAG identified that it would be important to have clarity on treatment eligibility for patients who have node-negative disease.
    a. The CGP agrees with the methods team that the efficacy of pertuzumab in node-negative patients should be considered unclear based on the APHINITY trial data. The amendment change that reduced the number of these patients in the trial and the low event rate (n=32 in the pertuzumab group versus n=29 in placebo group) precludes any conclusions on efficacy.
2) PAG is seeking guidance on the appropriateness of using pertuzumab plus trastuzumab post-surgery in patients who have received a few cycles of trastuzumab in combination with chemotherapy in the neoadjuvant setting pre-surgery.
    a. The CGP accepts that there may be net clinical benefit with adjuvant combination trastuzumab/pertuzumab therapy in node-positive patients who received chemotherapy and trastuzumab in the neoadjuvant setting. However, as there is no

evidence for use of single agent pertuzumab in the adjuvant setting, therapy would end with completion of trastuzumab. The CGP cannot comment on the statistical survival benefit of an abbreviated course of Pertuzumab therapy in the adjuvant context.

3) PAG is seeking guidance on adding pertuzumab for patients who are currently being treated with trastuzumab in the adjuvant setting who have not yet completed 1 year of adjuvant trastuzumab therapy (either currently receiving trastuzumab in combination with their chemotherapy, or trastuzumab monotherapy), if pertuzumab plus trastuzumab is recommended for reimbursement and when it is funded.
    a. The CGP is unable to comment on the benefit of partial therapy with combination trastuzumab/pertuzumab in the adjuvant setting, due to lack of clinical data.
4) Pertuzumab plus trastuzumab in combination with a taxane is first line treatment for HER2 positive metastatic breast cancer and is funded in all provinces. PAG is seeking guidance on whether the use of pertuzumab plus trastuzumab would be clinically appropriate in patients who develop metastatic disease and were treated with the combination in the adjuvant setting and, if appropriate, what time interval between the last dose in the adjuvant setting to starting treatment for metastatic disease would be reasonable.
    a. The CGP is unable to provide firm recommendations on the clinical appropriateness of combination trastuzumab/pertuzumab in the metastatic setting after previous exposure in the adjuvant setting, due to lack of data. Clinical judgement is advised.

1.3 Conclusions

The submitter has defined early stage, HER2-positive breast cancer at high risk of recurrence as either 1) lymph node positive or 2) hormone receptor negative disease. These two subgroups are the focus of the pCODR requested reimbursement criteria.

1) Lymph-node positive subgroup

The CGP concluded that there is ***likely*** a small yet clinically meaningful net clinical benefit to pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy among patients diagnosed with lymph node positive, HER-2 positive breast cancer. This conclusion is based on evidence from a pre-defined subgroup analysis from the APHINITY clinical trial, demonstrating a significant improvement in IDFS among patients diagnosed with node positive disease who underwent treatment with combination trastuzumab/pertuzumab. Comparatively, no significant improvement in IDFS was noted amongst patients in the lymph node-negative subgroup. The CGP concluded that the safety of pertuzumab/trastuzumab seemed tolerable and that chemotherapy might have contributed to some adverse events. Overall the safety profile was as expected and similar to the experience with this drug in the metastatic setting. The higher risk for primary cardiac events with pertuzumab/trastuzumab speaks to the need for monitoring and possible intervention during therapy. The CGP agreed that the improvements in IDFS observed with pertuzumab/trastuzumab are important in this patient population as clinically, node positive disease has been traditionally considered at higher risk for disease recurrence, due to the higher stage of disease (i.e. tumour burden) at presentation. More effective and less toxic therapies which improve survival rates are urgently required in this population.

In their feedback on the initial recommendation one PAG member noted that their tumour group disagreed with pERC's initial recommendation. The tumour group suggested that pertuzumab, trastuzumab, and chemotherapy could benefit a high risk group (3+ nodes and locally advanced

population [Stage III]) treated with a neoadjuvant approach. It was also noted that treating a high-risk group would reduce the number needed to treat and could prevent distant recurrences resulting in spending less money on treatment for metastatic breast cancer. In response to the tumour group's feedback, the CGP noted that the initial CGP recommendation stated that there is likely a small yet clinically meaningful net overall clinical benefit to pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy in patients diagnosed with lymph node positive, HER-2 positive early breast cancer. This CGP's recommendation applies to node-positive patients, regardless of the number of positive lymph nodes. The CGP agreed that additional analyses to further study the 3+ nodes subpopulation in the APHINITY trial would be underpowered and prone to error; hence the CGP could not make a recommendation on this specific subgroup.

2) Hormone-receptor negative subgroup

The CGP concluded that there is ***not*** a net clinical benefit to pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy among patients diagnosed with hormone-receptor negative, HER-2 positive breast cancer. This conclusion is based on evidence from a pre-defined subgroup analysis from the APHINITY clinical trial. While the results in the hormone-receptor negative subgroup demonstrated a treatment effect that favored pertuzumab-trastuzumab, the difference in IDFS was not statically significant. The CGP noted that the observed treatment effect could be the result of an interaction with lymph-node status, as the majority of patients in the hormone-receptor negative subgroup also had lymph-node positive disease. Based on the subgroup analyses results, presented in APHINITY, the CGP could not conclude that patients in the HR-negative subgroup are more likely to benefit from pertuzumab in combination with trastuzumab and chemotherapy than other subgroups. Further, it has not been established whether the definition of high risk HER2 positive breast cancers includes all patients with hormone receptor negative tumours, as the main biological driver of risk in this population is considered to be HER2 overexpression.

In making this conclusion the Clinical Guidance Panel also considered that:

1-The CGP acknowledges that the subgroup analysis was not corrected for multiple statistical comparisons, which may increase the rate of false positive results. The CGP also acknowledges that the primary analysis was conducted relatively early with a low number of patients experiencing an event, given that patients with early breast cancer may relapse after many years. Results may be updated pending subsequent analysis (next analysis due in 2.5 years, and ending at 10 years of follow-up).

2- The CGP accepts the assertion that evidence of net clinical benefit in patient with node positive disease is generalizable to patients who would start the 18 cycles of treatment in the neoadjuvant setting (i.e., 4 cycles before surgery) and have the balance of up to the maximum dose of 18 cycles after surgery. This assertion is based on the accepted clinical endpoint of IDFS, which was distinct from the endpoint of pCR used in the NeoSphere trial[16]. The CGP cautions against restricting the use of combination trastuzumab/pertuzumab therapy in node positive patients in the neoadjuvant setting.

3-The CGP does not support generalizing the study results to hormone receptor negative HER2-positive breast cancers less than 1 cm in size. It has not been established that these tumours are considered high risk, and data from APHINITY did not support pertuzumab in this subgroup. However, the CGP supports generalizing the study results to node-positive HER2 positive breast cancers less than 1 cm in size, as the driver of risk in these patients is node positive disease, not so much the primary tumour size.

4-The CGP acknowledges that the use of a modified invasive DFS endpoint limits interpretation of the treatment benefit, by providing a more conservative estimate of effect. However, in the absence of mature overall survival data, the CGP accepts this endpoint for decision making, and the results are therefore generalizable to Canadian clinical practice.

5-At this juncture, the CGP cannot make a determination of net overall survival benefit, due to immature OS data.

In their feedback on the initial recommendation, the submitter asked that pERC takes into consideration that a proven difference in overall survival at the time of the primary IDFS analysis is an unreasonable expectation, because:

- HER2-positive early breast cancer patients may relapse after many years and thus it takes longer to observe a large magnitude of IDFS or OS benefit with the addition of pertuzumab;
- At the time of the primary analysis, the adjusted two-sided alpha level for the first OS interim analysis was <0.00001, with cumulative power of 0%. Only the final OS analysis will have cumulative power of 80% (two-sided alpha level of 0.0453) to detect an OS hazard ratio of 0.8. This final OS analysis is event-driven once 640 study deaths have occurred, estimated to be 9-10 years after last patient randomized (i.e. 2023).
- Even with sufficient follow-up, the OS results may be confounded by post-trial therapies.
- Pre-specified subgroup analyses will again be descriptive.

The CGP agreed with the submitter that a proven OS benefit at this time is an unreasonable expectation. Further, the CGP reiterated that in the absence of an OS benefit, the surrogate endpoint of IDFS was likely a reasonable endpoint for decision making and that the CGP's conclusion of a likely small yet clinically meaningful net overall clinical benefit to pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy among patients in the lymph node positive subgroup holds, notwithstanding the immature OS data at this point. The CGP noted, that given patients with early breast cancer may relapse after many years, it seemed sensible to confirm the results with more mature OS data at the protocol pre-specified time. However, the CGP acknowledged that post-progression therapies may eliminate the OS benefit of the pertuzumab combination.

2 BACKGROUND CLINICAL INFORMATION

The section was prepared by the pCODR Breast Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Breast Cancer is a commonly diagnosed malignancy in Canadian women, with 26,300 new cases diagnosed in 2017.[12] Approximately 1 in 8 women will be diagnosed with breast cancer in their lifetime.[12] Fortunately, the majority of these cases represent early stage, potentially curable disease. Improved screening techniques, earlier detection, and more effective systemic therapy have all contributed to improved breast cancer outcomes.

A proportion of breast cancers (15-30%) overexpress HER2/neu, an epithelial growth factor receptor.[22] Her2/neu (referred to hereafter as HER2) is a transmembrane receptor tyrosine kinase in the ERBB family. HER2 binds an extracellular signalling ligand, triggering hetero/homodimerization with other receptors in the HER family, and auto-phosphorylation of cytoplasmic tyrosine residues. Ultimately, this process initiates a downstream signalling cascade, leading to growth, differentiation, and survival of cells. HER2 overexpression leads to excessive stimulation of this signaling pathway, leading to uncontrolled growth, reduced apoptosis, and metastasis of malignant cells[13] HER2 overexpression has historically been associated with a more aggressive disease course, with earlier metastatic potential, and a predilection for metastasis to the central nervous system. HER2 overexpression has not only been associated with breast cancer, but also with gastroesophageal, lung, ovarian, and serous endometrial tumours.

2.2 Accepted Clinical Practice

The administration of trastuzumab (Herceptin, Roche), an anti-HER2 monoclonal antibody, in combination with adjuvant chemotherapy, has significantly reduced the risk of disease recurrence in HER2 overexpressed breast carcinoma. Trastuzumab binds the extracellular domain of the HER2 receptor, preventing homodimerization with other HER2 receptors, and subsequent downstream auto- phosphorylation of intracellular tyrosine domains. Trastuzumab was initially approved in 1998 for treatment of HER2 positive metastatic disease.[22] This indication was expanded by the US Food Drug Administration (FDA) for the treatment of early breast cancer (EBC) in 2004. The current standard of care therapy for HER2 positive EBC is 12 months of adjuvant trastuzumab, in combination with anthracycline and/or taxane-based chemotherapy.[13,23] While trastuzumab is generally well tolerated, it is associated with cardiac toxicity, such as cardiomyopathy, decreased ejection fraction, and in severe cases, signs/symptoms of congestive heart failure.[23] This cardiac toxicity is hypothesized to be related to impairment of normal HER2-mediated cellular repair pathways, and is often reversible with discontinuation of therapy and medical management of cardiomyopathy.[24]

Recently, Pertuzumab (Perjeta, Roche) has been approved for the treatment of metastatic HER2 positive breast cancer[14,15], as well as management of locally-advanced disease.[16,17] Pertuzumab is a monoclonal antibody which binds a separate and distinct epitope on the extracellular domain of HER2, preventing heterodimerization with HER3, and subsequent downstream activation of the tyrosine kinase pathway. The combination of trastuzumab and pertuzumab has been demonstrated to significantly improve median overall survival in patients with metastatic HER2 positive breast cancer, from 40.8 months (with trastuzumab alone) to 56.5 months (with combination therapy).[15] The addition of pertuzumab does not appear to substantially increase the risk of cardiac toxicity, when compared to use of trastuzumab alone.[19] In the neoadjuvant setting, combination trastuzumab/pertuzumab demonstrated a significant improvement in pathologic complete response rate (pCR) as compared to trastuzumab-based therapy.[16,17] Unfortunately,

current neoadjuvant trastuzumab/pertuzumab trials have not been sufficiently powered to evaluate differences in survival outcomes. Although pCR is associated with improved survival among specific breast cancer subtypes, response to neoadjuvant chemotherapy is not a validated surrogate endpoint for disease-free or overall survival in breast cancer.[11] In 2015, pCODR reviewed the use of pertuzumab in combination with trastuzumab in the neoadjuvant setting[9], and concluded that there was insufficient evidence to support a claim of net clinical benefit for this combination for patients with early operable, locally advanced, or inflammatory breast cancer.

In 2013, combination trastuzumab/pertuzumab was approved by the FDA for the following indications[25]:

1. Use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
2. Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication is based on demonstration of an improvement in pathological complete response rate.

A recent phase III trial comparing combination adjuvant trastuzumab/pertuzumab to trastuzumab/placebo has demonstrated an improvement in invasive disease-free survival (IDFS) among patients with surgically resected HER2-positive early stage breast cancer.[20] However, overall survival results are not yet mature. The combination of trastuzumab and pertuzumab was FDA approved in 2017 for the adjuvant treatment of patients with HER2-positive breast cancer at high risk of recurrence. The European Medicines Agency (EMA) also approved the adjuvant indication in April 2018.

2.3 Evidence-Based Considerations for a Funding Population

The evidence-based population suitable for consideration of combination trastuzumab and pertuzumab in the early breast cancer setting is similar to the population studied in the B-31/HERA[13] and N9831[23] adjuvant trastuzumab trials, as well as the more recent APHINITY adjuvant trastuzumab/pertuzumab trial.[13,20,23] This population includes:

1. Histologically confirmed, completely excised invasive breast cancer with HER2 overexpression or HER2 amplification[26]
2. Adequate baseline hepatic, renal, and bone marrow function
3. Use of adequate non–hormone-based contraceptive measures, if indicated
4. No distant metastases, previous invasive breast carcinoma, or a neoplasm not involving the breast, except for curatively treated basal-cell or squamous-cell carcinoma of the skin or in situ carcinoma of the cervix
5. Early stage disease - Stage IIB or earlier (i.e. T3N0M0 or T2N1M0)
6. Normal left ventricular ejection fraction (LVEF) (≥55 percent as measured on echocardiography or multiple gated acquisition [MUGA] scanning)

Additional inclusion criteria may be considered, as per the APHINITY trial:

1. A tumour diameter greater than 1cm
2. Tumours between 0.5 and 1cm, if one additional risk factor was present (grade 3, ER/PR negative, or age <35).

Patients with prior mediastinal irradiation (except internal mammary-node irradiation for the present breast cancer), previous exposure to anthracycline chemotherapy, documented congestive

heart failure, coronary artery disease with previous Q-wave myocardial infarction, angina pectoris requiring medication, uncontrolled hypertension, clinically significant valvular disease, and unstable arrhythmias were excluded from these studies, and may not be candidates for adjuvant pertuzumab therapy.

2.4 Other Patient Populations in Whom the Drug May Be Used

The following patient groups may also be considered when generalizing the results of this review:

1. Patients with lymph node positive, HER2 positive breast cancer considered for neoadjuvant chemotherapy. This group was the focus of a previous pCODR review. A negative funding recommendation was given citing a lack of improved survival data. Unfortunately, the neoadjuvant trials were underpowered. We will likely not get sufficiently powered trials to evaluate survival in this setting. Therefore, we may need to consider whether data from this current review could be generalized to the node positive neoadjuvant setting. The CGP accepts the assertion that evidence of net clinical benefit in patients with node positive disease is generalizable to patients who would start the 18 cycles of treatment in the neoadjuvant setting (i.e., 4 cycles before surgery) and have the balance of up to the maximum dose of 18 cycles after surgery. The FDA has already made an approval in the neoadjuvant setting.
2. Inflammatory breast cancer
3. Male breast cancer

Patients with advanced HER2 positive metastatic breast cancer have also been found to benefit from trastuzumab/pertuzumab as 1st line therapy in combination with chemotherapy. This review will focus on the benefits of trastuzumab/pertuzumab in the adjuvant setting among early stage breast cancer patients.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer Canada provided patient input on pertuzumab-trastuzumab combo pack for early stage breast cancer. The input by Rethink Breast Cancer was submitted after pCODR's pre-specified deadline and, therefore, has not been included in this summary. CBCN's input is summarized below:

Information provided by CBCN was collected from a survey, key informant interviews, and a review:

CBCN's 2017 Breast Cancer Patient Survey: Using the membership databases of CBCN and other patient organizations, an online survey (in English and French) was distributed to patients living with breast cancer. Survey questions comprised of a combination of scoring options and free form commentary. A total of 278 early-stage breast cancer patients responded to the survey; of those, 33 patients had early-stage, HER2 (human epidermal growth factor receptor 2)-positive breast cancer. For the purpose of this submission, CBCN specifically reported the data provided by the 33 survey respondents who had early-stage, HER2-positive breast cancer; none of these respondents had direct experience with pertuzumab-trastuzumab. The baseline characteristics of these survey participants are summarized in Table 3.1.

All 33 respondents were female, with the greatest proportion being from the province of Ontario (18.2%), followed by Saskatchewan (15.2%), Manitoba (9.1%), and Quebec (9.1%), British Columbia (6.1%), and New Brunswick (6.1%), and one respondent each from Alberta, Prince Edward Island, Newfoundland, and Nova Scotia. The remaining eight respondents did not specify their province of residence. More than 50% of the respondents reported English, and 15% reported French as their first language. Close to 80% of the respondents were between the ages of 40-59 when diagnosed. Most respondents were in a relationship (66.7%), while three respondents declared themselves as single, and eight respondents did not specify their relationship status. Most of the respondents (28/33) had children; of those, 12 had children aged 20 years or older, six had children between the ages of 13-19, five had children 2-5 years of age, three had children below 1 year, and two had children between 6-12 years of age.

Table 3.1: Demographic characteristics of the CBCN survey respondents (HER2-positive breast cancer patients; n=33)

Baseline variables	n (%)
Age at diagnosis (years)	
30-39	4 (12.1)
40-49	15 (45.5)
50-59	11 (33.3)
60-69	3 (9.1)
Province of residence	
Ontario	6 (18.2)
Saskatchewan	5 (15.2)
Manitoba	3 (9.1)
Quebec	3 (9.1)
British Columbia	2 (6.1)
New Brunswick	2 (6.1)
Alberta	1 (3.0)
Prince Edward Island	1 (3.0)
Newfoundland	1 (3.0)
Nova Scotia	1 (3.0)
Not specified	8 (24.2)
First language	
English	17 (51.5)
French	5 (15.2)
Other (Cantonese, Polish and Serbo-Croatian)	3 (9.1)

Baseline variables	n (%)
Not specified	8 (24.2)
Family relationship status	
In relationship	22 (66.7)
Single	3 (9.1)
Not specified	8 (24.2)

Key informant interviews: Phone interviews were conducted in March 2018 with two Canadian patients with early stage, HER2-positive breast cancer who had direct experience with the treatment under review:

- A 42-year old patient with HER2-positive, HR-negative, early-stage breast cancer patient who had been on treatment since December 2017. She accessed prescribed treatment through her cancer centre in Alberta through a combination of private insurance coverage, manufacturer's patient assistance program and paying out of pocket. She previously had been treated with an ACTH chemotherapy regimen (doxorubicin hydrochloride (Adriamycin) and cyclophosphamide, followed by paclitaxel (Taxol) and trastuzumab (Herceptin)).
- A 49-year old patient with HER2-positive, HR-negative, inflammatory, early-stage breast cancer patient who had been on treatment since March 2018. She accessed prescribed treatment through her cancer centre in Alberta through a combination of private insurance coverage and manufacturer's patient assistance program. Pertuzumab-trastuzumab was the first treatment she had been prescribed for her breast cancer; however, she had since chosen to stop treatment in April 2018.

Printed sources: A review was conducted of current studies and grey literature to identify issues and experiences that are commonly shared among many women living with breast cancer.

From a patient's perspective, the diagnosis of HER2-positive breast cancer, as well as the treatments used, could impact both the emotional and physical well-being. CBCN noted that most patients currently receive a combination of the anti-HER2 therapy, trastuzumab, in addition to standard chemotherapy. CBCN reported that some of the side effects of HER2 positive breast cancer and the therapies used to manage this disease include: cardiac toxicity, fever, cough, muscle pain, fatigue, diarrhea and nausea. Many of these symptoms have the ability to impact daily life, primarily: fatigue, pain and nausea. According to CBCN, the financial burden associated with living with breast cancer extends far beyond any loss of income during a temporary or permanent absence from employment. In addition to the loss of income during illness, breast cancer patients can incur substantial costs associated with treatment and disease management

According to CBCN it is important for patients to have access to therapies that will extend their life expectancy without significantly increasing side effects that will negatively impact their daily lives. Also, as HER2-positive breast cancers are shown to be at higher risk of recurrence than HER2 negative tumours, the goal of therapy is to target cancer cells in the body and reduce the risk of disease recurrence. According to CBCN the following factors were shown to affect patients' choice of treatment options (in order of importance): effectiveness of the treatment, reducing the risk of recurrence, maintaining quality of life and maintaining mobility, maintain productivity, minimal side effects, minimal medical appointments and ability to continue childcare duties.

In total, two patient respondents indicated having experience with the pertuzumab and trastuzumab combination. Respondents noted that it was difficult for them to determine if the side effects experienced were from the chemotherapy or from the combination therapy. One patient experienced mild nausea, taste changes, fatigue, low white blood cell count and mouth cankers, but ranked her quality of life as medium and tolerable. The other patient experienced nausea, chills, diarrhea, and hunger, and chose to suspend her treatment (after approximately one month of treatment) but maintains that her quality of life always resumed, as she never had

more than two days in bad health. Relative to the experienced side effects, participants had an overall positive attitude towards the combination treatment, reporting gratitude at having access to this treatment and expressed that more women should have access to this treatment.

Please see below for a summary of specific input received from CBCN.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with HER2 Positive Early Breast Cancer

CBCN noted that the diagnosis of HER2-positive breast cancer, as well as the treatments used, could impact both the emotional and physical well-being of a patient. Some of the side effects of HER2 positive breast cancer and the therapies used to manage this disease include: cardiac toxicity, fever, cough, muscle pain, fatigue, diarrhea and nausea. Many of these symptoms have the ability to impact daily life, primarily: fatigue, pain and nausea. Therefore it is important for patients to have access to therapies that will extend their life expectancy without significantly increasing side effects that will negatively impact their daily lives. CBCN also indicated that, HER2-positive breast cancers (approximately 20%-30% of all diagnosed breast cancer cases in Canada) are more aggressive and less responsive to hormone therapies used for other breast cancers; and that patients affected by this disease have fewer treatment options available to them. Referring to the results of existing clinical studies, CBCN emphasised the importance of providing patients access to therapies that would extend their life expectancy without significantly increasing side effects.

In the CBCN's 2017 Breast Cancer Patient Survey, eight of the 33 respondents were diagnosed with Stage 1 cancer, 14 with Stage 2, and seven with Stage 3. Four patients did not specify their stage. Only one patient had experienced a recurrence at Stage 2. Most patients had undergone surgery (28 out of the 33 respondents), radiation therapy (22 out of 33 respondents) and chemotherapy (22 out of 33 respondents) as part of their overall breast cancer treatment.

3.1.2 Patients' Experiences with Current Therapy for HER2 Positive Early Breast Cancer

CBCN acknowledged that managing early-stage HER2-positive breast cancer is always a challenge as patients have more limited treatment options available to them. As HER2-positive breast cancers are shown to be in a higher risk of recurrence than HER2 negative tumours, the goal of therapy is to target cancer cells in the body and reduce the risk of disease recurrence. CBCN noted that most patients currently receive a combination of the anti-HER2 therapy, trastuzumab, in addition to standard chemotherapy. However, none of the patients who participated in the CBCN survey had direct experience with the treatment under review (i.e., pertuzumab-trastuzumab combination therapy).

According to CBCN, the financial burden associated with living with breast cancer extends far beyond any loss of income during a temporary or permanent absence from employment. In addition to the loss of income during illness, breast cancer patients can incur substantial costs associated with treatment and disease management. Referring to the results of existing research on the financial impact of breast cancer[27] CBCN indicated that 80% of breast cancer patients report a financial impact due to their illness; 44% of patients have used their savings; and 27% have taken on debt to cover costs.

In the CBCN's 2017 Breast Cancer Patient Survey, nine of the 33 HER2-positive, early stage breast cancer patients stated that they had experienced a very large financial impact as

result of their diagnosis, and 10 stated that they had experienced some financial impact from their diagnosis. While at the time of their diagnosis, 14 respondents were employed full-time, six were employed part–time, two were self-employed and three were retired; their employment status changed significantly following the diagnosis of breast cancer. At the time of the survey, only seven patient respondents remained employed full-time, nine were retired, two were employed part-time, and three were on disability. One patient respondent stated [undergoing a breast cancer diagnosis and treatment was]:

"*Very hard on my family...had to return to work still not feeling strong enough...very hard ...when you're sick you don't need this stress on top of everything else…*".

According to CBCN, access to private insurance coverage and support medications contribute to the financial burden experienced by patients and impose barriers to getting required treatment. While 26 of the 33 patients surveyed reported having private insurance coverage, seven reported challenges accessing medications not publicly reimbursed. Twenty patients stated that they had been prescribed support medications as part of their treatment, and nine patients stated that their support medications were not provincially reimbursed. Instead, respondents stated that they had to use private insurance (15 respondents) or pay out of pocket (7 respondents) to access medications they had been prescribed.

In CBNC's survey of 33 HER2-positive, early-stage breast cancer patients, the following factors were shown to affect patients' choice of the treatment options:

- Effectiveness of the treatment, with 27 of 33 patients declaring it was very important to them. One patient stated:

  "I just wanted to make sure they did everything to get rid of the cancer."

- Reducing the risk of recurrence, with 23 of 33 patients declaring it as very important, one patient as somewhat important, and two patients as important. One patient stated:

  "I only wanted to reduce my risk of recurrence as much as possible. Everything else was secondary."

- Maintaining quality of life, with 15 patients declaring it as very important, three patients as somewhat important, and six patients as important. One patient stated:

  " My quality of life during and after treatment was the biggest issue for me."

- Maintaining mobility, with 14 patients declaring it as very important, five patients as somewhat important, and seven patients as important.

- Maintaining productivity, with nine patients declaring it as very important, six patients as somewhat important, and seven patients as important.

- Minimal side effects, with eight patients ranking it as very important, 10 patients as somewhat important, and eight patients as important. One patient stated:

  "I was willing to do whatever was best to rid myself of the cancer. I could deal with the side effects and disruption in my life for the long term good."

- Minimal medical appointments, with five patients ranking it as very important, five patients as somewhat important, and five patients as important.

- Ability to continue childcare duties, with three patients declaring it as very important, and19 patients as not important. CBCN noted that the majority of patients who responded to the survey had children over the age of 20 years; therefore, childcare was not a concern during their treatment. However, for patients with younger children, childcare could be a much more critical factor in determining their treatment options. One patient stated:

  "I am a mother to 3 children. I wanted to be aggressive in order to increase my chances of survival."

3.1.3 Impact of HER2 Positive Early Breast Cancer and Current Therapy on Caregivers

CBCN noted the financial burden placed on early-stage breast cancer patients and their families. However, no further information was provided in the submitted input regarding the impact that diagnosis and treatment of early stage breast cancer may have on caregivers.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Pertuzumab-Trastuzumab Combination

CBCN conducted interviews with Canadian patients with different levels of experience with the treatment (as described earlier in this section). Both patients expressed their gratitude at having access to this treatment. Patient 1 noted her personal satisfaction with the treatment and both patients noted their oncologists' confidence in using the therapy.

"*I chose this treatment because it was the most effective treatment to kill the cancer. I wanted the option of using both agents. I feel very lucky to be able to do both*"-Patient 1

"*I didn't consider any other treatment options. I relied on my physician's knowledge and expertise and he thought this was the best option for me. I am grateful to have access to this treatment. I have inflammatory breast cancer-so it was very aggressive and I'm so happy to have that access."* -Patient 2

Both patients noted that it was very difficult for them to determine if the side effects they experienced from combined treatment were from the chemotherapy or from the pertuzumab-trastuzumab therapy. The patients had differing experiences with the tolerability of their side effects. Patient 1 experienced mild nausea, taste changes, fatigue, low white blood cell count and mouth cankers, but ranked her quality of life as medium and tolerable. Patient 2 experienced nausea, chills, diarrhea, and hunger, and chose to suspend her treatment (after approximately one month of treatment) but maintains that her quality of life always resumed, as she never had more than two days in bad health.

"*It's never pleasant to go through cancer treatment, but overall I would say my quality of life is a medium-it's tolerable!*"- Patient 1

"*Despite my strong side effects, I would still say that overall I still managed. After a few days, I could move around, I never spent more than 2 days in bad health."* –Patient 2

In terms of potential alternatives to the treatment, Patient 1 mentioned that without this treatment, she would have likely been left with only pertuzumab-trastuzumab or chemotherapy as an alternative treatment, while Patient 2 was uncertain of what her other treatment options may be.

The patients interviewed also discussed the impact that access to pertuzumab-trastuzumab had on their quality of life and ability to be productive.

"*I chose this treatment to prevent recurrence. Nobody wants to die. I wanted more time to spend with family and loved ones. I think more women should be able to have the option to use it as part of their treatment.*"-Patient 1

"*I had a fear of recurrence, and fear of my diagnosis. I was told my cancer was aggressive and my husband really wanted me to try this option and give it a chance. Even though it didn't end up being right for me, if the doctors are offering it and you can find a way to pay for it- I think patients should do it. Economic decisions should not be the reason people can't access treatment. Healthcare is a given, it should not be treated as a privilege*." -Patient 2

3.3 Additional Information

No additional information was provided.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group 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) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarity on eligible patient population
- Use of the combination post-surgery in patients who have received a few cycles of trastuzumab with chemotherapy in the neoadjuvant setting before surgery

Economic factors:

- Drug wastage for trastuzumab (more likely in small centres where vial sharing is minimal)
- Reimbursement of only the combination package of pertuzumab and trastuzumab, rather than the single agent pertuzumab vial

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that current treatment for adjuvant treatment of early breast cancer is trastuzumab with chemotherapy.

4.2 Eligible Patient Population

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

- locally advanced or inflammatory breast cancer,
- ECOG performance status greater than 1,
- Node-negative disease,
- Small tumors less than 1 cm.

PAG is seeking guidance on the appropriateness of using pertuzumab plus trastuzumab post-surgery in patients who have received a few cycles of trastuzumab in combination with chemotherapy in the neoadjuvant setting pre-surgery.

Previously, pERC did not recommend reimbursement of pertuzumab in combination with trastuzumab and chemotherapy for neoadjuvant treatment of HER2-positive primary operable or locally advanced/inflammatory breast cancer. Pertuzumab plus trastuzumab is not funded in any province for neoadjuvant treatment. PAG noted that this review is for adjuvant treatment of non-metastatic HER2-positive operable early breast cancer and that

the recommendation to not reimburse for neoadjuvant treatment would still be applicable.

4.3 Implementation Factors

Pertuzumab is an add-on drug to current treatment with trastuzumab plus chemotherapy followed by trastuzumab alone for up to 18 cycles. There would be additional pharmacy preparation, nursing administration and chemotherapy chair time for the pertuzumab.

PAG identified that this submission is for pertuzumab packaged as a combination kit with one vial of trastuzumab. Although there would be no drug wastage for pertuzumab as the 420mg flat dose is available as one vial in the kit, PAG noted that there could be some drug wastage of trastuzumab in smaller centres where vial sharing opportunities may be limited, as the dose is weight based and the kit contains one vial of 440mg trastuzumab.

PAG is also seeking guidance on adding pertuzumab for patients who are currently being treated with trastuzumab in the adjuvant setting who have not yet completed 1 year of adjuvant trastuzumab therapy (either currently receiving trastuzumab in combination with their chemotherapy, or trastuzumab monotherapy), if pertuzumab plus trastuzumab is recommended for reimbursement and when it is funded.

.

4.4 Sequencing and Priority of Treatments

Pertuzumab plus trastuzumab in combination with a taxane is first line treatment for HER2 positive metastatic breast cancer and is funded in all provinces. PAG is seeking guidance on the whether the use pertuzumab plus trastuzumab would be clinically appropriate in patients who develop metastatic disease and were treated with the combination in the adjuvant setting and, if appropriate, what time interval between the last dose in the adjuvant setting to starting treatment for metastatic disease would be reasonable.

4.5 Companion Diagnostic Testing

Her-2 testing is already available.

4.6 Additional Information

This submission is only for pertuzumab packaged as a combination with trastuzumab (Perjeta-Herceptin kit). PAG identified that pertuzumab is available in Canada as a single vial and wants to strongly express that pertuzumab single vial would be preferred for implementation, if recommended for reimbursement.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided for pertuzumab and trastuzumab for the adjuvant treatment of patients with early breast cancer.

This treatment is indicated for human epidermal growth factor receptor 2 (HER2)-positive early breast cancer patients at high risk of recurrence, defined as either node-positive or hormone receptor-negative disease. In terms of the clinical benefit, it was noted in the joint input that the improvement demonstrated in the node-positive patients was minimal in the APHINITY trial and that there was no real advantage in node-negative patients. While the clinicians acknowledged the benefit of pertuzumab and trastuzumab, when compared with placebo and trastuzumab for invasive disease-free survival in the APHINITY trial, they were unsure if the observed benefit is clinically meaningful given the lack of a significant difference in overall survival. In addition, the clinicians providing the joint input did not believe this treatment fills an unmet need because there are effective treatments available already, and the trial only demonstrated a modest improvement. It was noted by the individual clinician providing input that overall the trial results in the adjuvant setting were disappointing, however, selective use of this therapy could benefit higher risk populations including node positive patients. For clinical use, pertuzumab would be added in combination with trastuzumab and not sequentially. Companion diagnostic testing would include HER2 positive testing, which is already done as routine standard of practice.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s) for HER2 Positive Early Breast Cancer

The clinicians providing input indicated that trastuzumab + chemotherapy is the current standard treatment for the specified patient population.

More specifically, it was noted that the standard treatments in neo-adjuvant or adjuvant settings are TCH (docetaxel/carboplatin and Herceptin [trastuzumab]), anthracycline-containing regimens (AC-TH, FEC-TH) or TC (docetaxel/cyclophosphamide with Herceptin), and less commonly, weekly paclitaxel x 12 and Herceptin q3wk x one year.

5.2 Eligible Patient Population

In the joint CCO submission, it was noted that the APHINITY trial only examined the pertuzumab and trastuzumab combination for use in the adjuvant setting, and that there was no real advantage in node-negative patients and minimal improvements in node-positive patients. It was noted that it is unclear whether this indicates a survival advantage. As well, it was mentioned that use in the neoadjuvant setting was previously deliberated and received a negative funding recommendation in 2015.

The individual clinician providing input indicated that, in the adjuvant setting, approximately half the number of patients currently receiving standard combinations would be eligible, as the small benefit is worthwhile primarily in the node positive subset. Referring to NeoSphere trial, the clinician noted that where most HER2+ positive patients with clinical stage T2-4 (or any tumour size (T) node positive) are treated using standard chemo-Herceptin regimens, it would be expected that pertuzumab would be used in most or all cases given its significant beneficial effect on pathologic complete response rates.

5.3 Relevant to Clinical Practice

The clinicians providing input from the joint CCO input stated that the Drug Advisory Committee

(DAC) acknowledges the benefit of pertuzumab and trastuzumab, when compared with placebo and trastuzumab for invasive disease-free survival in the APHINITY trial, but the committee is not sure if the observed benefit is clinically meaningful given the lack of a significant difference in overall survival. It was also stated that the DAC recognizes that the combination would be nice to have, but is not enthusiastic about it at this time. It was suggested that a reassessment of the data be done when mature survival data becomes available.

The clinicians providing joint input from CCO stated that in the patient population in the APHINITY trial, there has been a large benefit observed with trastuzumab, whereas the benefit from the combination appears much more modest.

In terms of an unmet need, the clinicians providing input from the joint submission indicated that good treatment options currently exist for adjuvant HER2+ breast cancer and therefore this treatment does not fill an unmet need. Lastly, it was noted that there is no real advantage in node negative patients and minimal improvements in node positive patients, however, it is unclear whether this indicates a survival advantage.

The individual clinician providing input indicated that, in the neoadjuvant setting, a much better response rate was noted in their clinical observations, which often translated to improved cosmesis, the potential for breast sparing surgery instead of mastectomy, and potentially better long term outcomes (based on other studies linking pCR to long term DFS). The clinician added that the overall intention to treat results of the APHINITY trial were disappointing, but the selective use of pertuzumab trastuzumab in higher risk subsets, particularly node positive, would represent a significant benefit.

5.4 Sequencing and Priority of Treatments with Pertuzumab

The clinicians providing input from the joint CCO input reported that patients who receive pertuzumab-trastuzumab in the adjuvant setting would not receive the combination again in the metastatic setting. In addition, patients who progress would likely be given an alternative therapy, and it was mentioned that there are other drugs being evaluated in this space (e.g. neratinib).

The individual clinician providing input reported that pertuzumab would be used as an additional agent and not sequentially, and would not displace another agent.

5.5 Companion Diagnostic Testing

The clinicians providing input reported that companion diagnostic testing related to this treatment is already in place. This would include HER2 testing, which is already routine standard of practice. It was noted that HER2 positivity would be defined as 3+ by immunohistochemistry or Fluorescence In Situ Hybridization (FISH) positivity by accepted criteria.

5.6 Additional Information

It was noted by the individual clinician providing input that the benefits of this therapy would outweigh the harms (cost-related, and diarrhea), and would be compatible with patient values and goals. It was also noted that in the adjuvant setting, pertuzumab may not be beneficial in estrogen receptor positive and lymph node negative patient subsets.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of pertuzumab in combination with trastuzumab and chemotherapy as adjuvant treatment for HER2-positive early stage breast cancer at high-risk of recurrence. High-risk is defined as patients with either node-positive or hormone-receptor negative disease.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were not identified while developing the review protocol.

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. Studies were chosen for inclusion in the review based on the criteria in the table below. 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 randomized controlled trials	• Histologically confirmed, adequately excised, invasive HER2-positive early stage (1-3) breast cancer	• Pertuzumab combined with trastuzumab and chemotherapy	• Trastuzumab and chemotherapy	• OS
				• Distant recurrence
				• DFS
				• QOL
				• Safety
				  ○ Cardiac events
				  ○ GI toxicity including diarrhea

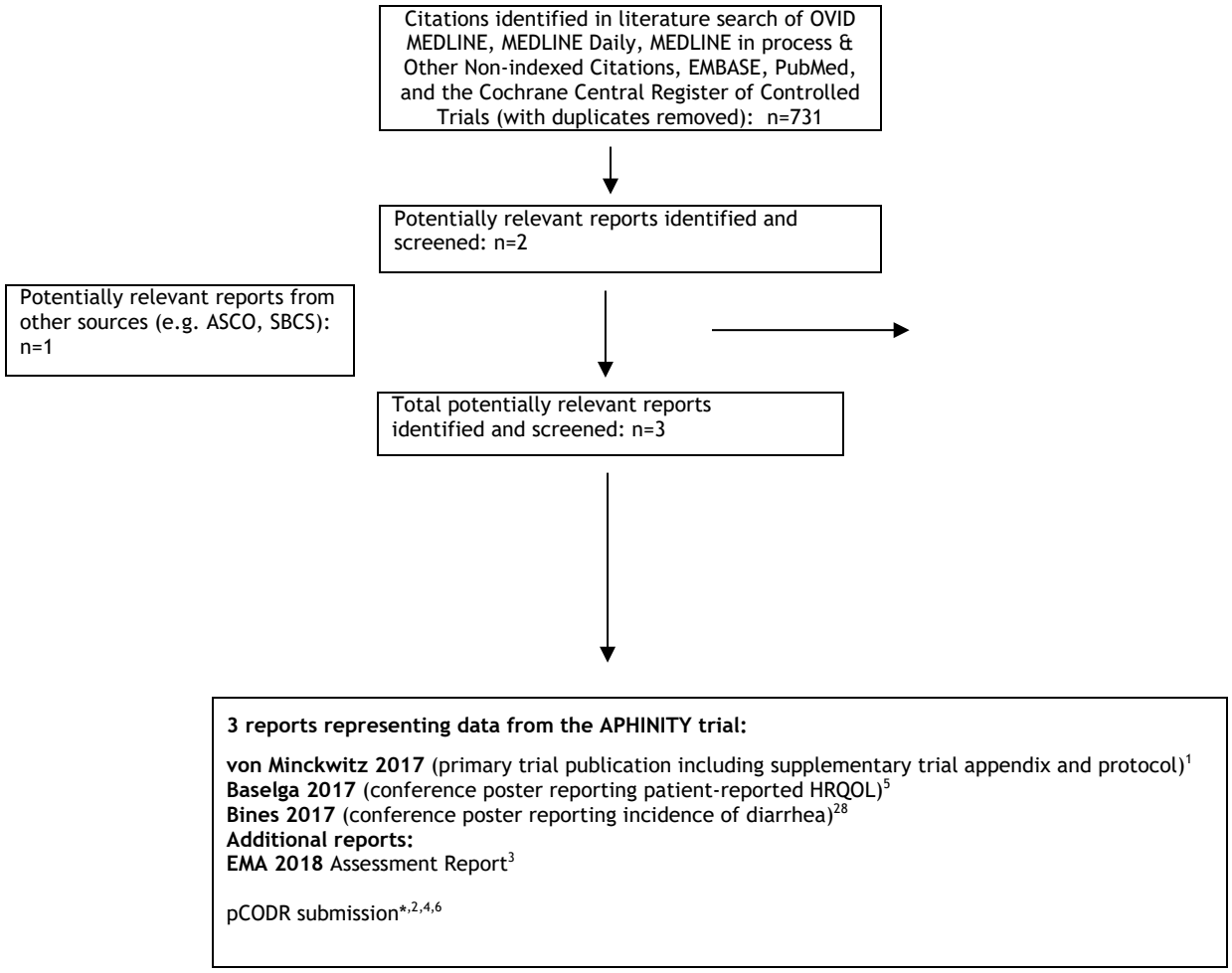
Abbreviations: DFS - disease free survival; GI - gastrointestinal; HER2 - human epidermal growth factor receptor 2; OS - overall survival; QOL - quality of life.				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).				

6.3 Results

6.3.1 Literature Search Results

Of the 782 potentially relevant reports identified, three reports were retrieved for full-text review and subsequently included in the pCODR systematic review.[1,5,28]

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Studies



**Note: Additional data related to the APHINITY trial were also obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

One RCT, APHINITY, was identified that met the eligibility criteria of the pCODR systematic review.[1] Characteristics of the trial are summarized in Table 4 and specific aspects of trial quality are summarized in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included APHINITY trial.[1]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes

APHINITY (NCT01358877)
 	
Phase 3, double-blind, placebo-controlled RCT with 1:1 randomization ratio
 	
N randomized=4805; N treated=4769
 	
549 centres in 43 countries[e] including Canada (23 centres; n=110)[2]
 	
Patient enrollment: November 2011 to August 2013
 	
Data cut-off date: December 19, 2016[29]
 	
Final Analysis Date: December 1, 2023[29]
 	
F. Hoffman La Roche/Genentech
	<u>Key Inclusion Criteria:</u>
	• Age ≥ 18 years
	• Newly diagnosed, non-metastatic, adequately excised (total mastectomy or breast conserving surgery), histologically confirmed invasive HER2-positive breast cancer[a]
	• Known HR status
	• Synchronous bilateral invasive disease if both lesions HER2-positive
	• Node-positive (any tumour size except T0, or node-negative (if tumour diameter >1 cm)[b]
	• Node-negative tumours[b] between 0.5 and 1 cm were also eligible if at least one of the following high-risk factors present:
	  ○ Histologic or nuclear grade 3
	  ○ Estrogen and progesterone HR negative
	  ○ Age < 35 years
	• ECOG 0-1
	• Interval between definitive surgery and first chemotherapy dose had to be within 8 weeks
	• Baseline left ventricular ejection fraction of at least 55%
	
	<u>Key Exclusion Criteria:</u>
	• Previous invasive breast cancer
	• Non-breast cancer within 5 years prior to randomization[c]
	• Any previous chemotherapy, radiotherapy, anti-HER2 therapy, or immunotherapy for cancer
	• Any concurrent serious
		Chemotherapy[d]
		+ trastuzumab
		(8 mg/kg loading dose then 6 mg/kg iv q 3 weeks)
		+ pertuzumab
		(840 mg loading dose then 420 mg iv q 3 weeks)
		
		versus
		
		Chemotherapy[d]
		+ trastuzumab
		(8 mg/kg loading dose then 6 mg/kg iv q 3 weeks)
		+ placebo
		(840 mg loading dose then 420 mg iv q 3 weeks)
		
		Treatment duration was a maximum of 18 cycles within one year in both groups
			<u>Primary:</u>
			• Invasive DFS
			
			<u>Secondary:</u>
			• OS
			• DFS
			• Invasive DFS (STEEP)
			• Relapse-free interval
			• Distant-relapse-free interval
			• HRQOL (EORTC QLQ-C30; EQ-5D)
			• Safety
			  ○ Cardiac events

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	diseases interfering with planned treatment including serious cardiac or CVD, or severe pulmonary conditions		

Abbreviations: CVD - cardiovascular disease; **EORTC QLQ-C30** - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; **EQ-5D** -EuroQOL 5-Dimensions; **DFS** - disease free survival; **HER2** - human epidermal growth factor receptor 2; **HR** - hormone receptor; **HRQOL** - health-related quality of life; **iv** - intravenous; **OS** - overall survival; **q** - every; **STEEP** - standardized definitions for efficacy endpoints in adjuvant breast cancer trials.

Notes:
[a] - HER2 status was centrally confirmed and defined as an immunohistochemical score of 3+ in more than 10% of immunoreactive cells or amplification of ERBB2 by in situ hybridization.
[b] - A protocol amendment, made after 3655 patients had undergone randomization, stipulated patients with node-negative disease were no longer eligible for enrollment in the trial due to an unexpected high number of node-negative patients randomized. The protocol amendment was made so the nodal status distribution in the trial reflected the distribution that had been anticipated when the trial was designed.
[c] - Except for the following: carcinoma in situ of the cervix or colon, melanoma in situ, and skin basal cell or squamous-cell carcinomas.
[d] - Chemotherapy was administered according to one of the following schedules: 3 or 4 cycles (every 3 weeks) of 5-fluorouracil plus either epirubicin or doxorubicin plus cyclophosphamide, followed by 3 or 4 cycles (every three weeks) of docetaxel or 12 weekly cycles of paclitaxel; 4 cycles (every 3 weeks or every 2 weeks) of cyclophosphamide plus either doxorubicin or epirubicin, followed by either 4 cycles (every 3 weeks) of docetaxel or 12 weekly cycles of paclitaxel; or 6 cycles (every 3 weeks) of docetaxel plus carboplatin.
E - Other participating countries: Argentina, Australia, Austria, Belgium, Bulgaria, Chile, China, Colombia, Croatia, Czech Republic, Denmark, El Salvador, France, Germany, Guatemala, Hong Kong, Hungry, Ireland, Israel, Italy, Japan, Mexico, Netherlands, New Zealand, Panama, Peru, Philippines, Poland, Romania, Russia, South Africa, South Korea, Slovenia, Spain, Sweden, Switzerland, Taiwan, Thailand, Ukraine, United Kingdom, and United States.[29]

a) Trials

Trial Design

APHINITY is an ongoing, international, multi-centre, phase 3, double-blind, placebo-controlled RCT comparing the efficacy and safety of pertuzumab-trastuzumab versus placebo-trastuzumab, both combined with chemotherapy, as adjuvant treatment after surgery for patients with HER2-positive early stage breast cancer.[1] The design of the APHINITY trial is depicted in Figure 2. Prior to the enrollment of individual patients into the trial, the protocol stipulated the following:

- HER2 status of breast tumours be confirmed by central laboratory
- Chemotherapy regimen be selected from a list of available options (Table 5)
- Each participating centre have a policy on the use of RT and HT that complied with guidelines set out in the trial protocol. A trial amendment (version D) later permitted adjuvant RT and HT to be administered according to standard local practice. Adjuvant HT (HR positive patients) and RT could start at the end of chemotherapy.
- Randomized treatment had to start within eight weeks of surgery, with targeted treatment commencing at the start of taxane chemotherapy

The trial enrolled patients from 549 centres in 43 countries including Canada (23 sites; n=110).[2] Just over half of trial patients (approximately 53%) were from centres in Canada, Western Europe, Australia/New Zealand, and South Africa; refer to Table 4 (notes section) for the complete list of participating countries.

Funding

The trial Sponsor, Hoffman La Roche/Genentech, designed the trial in consultation with the trial investigators, and had an active role in trial conduct including data collection and analysis, and manuscript preparation.

Eligibility Criteria

Patients included in the APHINITY trial met the following key criteria:

- Age ≥ 18 years
- Newly diagnosed, non-metastatic, adequately excised (total mastectomy or breast conserving surgery), histologically confirmed invasive HER2-positive breast cancer
- HR status known
- Node-positive (pN ≥1; any tumour size except T0) or node-negative (pN0; any tumour diameter >1 cm)
- Node-negative tumours between 0.5 and 1 cm were also eligible if at least one of the following high-risk factors were present:
    - Histologic or nuclear grade 3
    - Estrogen and progesterone HR negative
    - Age < 35 years
- ECOG performance status of 0-1
- Patients treated previously with chemotherapy (including therapy administered in the neoadjuvant setting), radiotherapy, anti-HER2 therapy, or immunotherapy were excluded

For a more detailed list of the key eligibility criteria used in the trial refer to Table 4.

Outcomes

The primary outcome of the trial was invasive DFS (IDFS), a composite endpoint, defined as the time from randomization until the date of the first occurrence of one of the following invasive disease events: recurrence of ipsilateral invasive tumour, recurrence of ipsilateral locoregional invasive disease, distant recurrence, contralateral invasive breast cancer, or death from any cause. This definition of IDFS is different from the established STEEP definition (Hudis et al, 2007)[21] by excluding second primary invasive non-breast cancers. Both definitions exclude in situ carcinomas, including DCIS and LCIS (non-invasive breast cancers), and non-melanoma skin cancers.[3]

The secondary outcomes of the trial included IDFS (STEEP), DFS (includes second primary invasive non-breast cancers and non-invasive breast cancer), OS, relapse-free interval, and distant relapse-free interval. For the full definitions of the secondary outcomes in the trial refer to the bottom of Table 8 (notes section). The STEEP definition of IDFS is often the primary outcome of adjuvant breast cancer trials as it takes into consideration the difficultly in distinguishing second primary invasive cancers from breast cancer metastases, and further, that second malignancies can be related to treatment.[21] Patient-reported HRQOL was considered an exploratory outcome of the trial.

Disease Assessment

Prior to enrollment, patient tumours had to be confirmed as HER2-positive by a central laboratory. A mammogram or breast MRI and chest x-ray/CT/MRI/PET scan were to be completed within the six months prior to randomization. After the screening period of the trial, mammography or MRI were then repeated at yearly intervals, and chest x-ray/CT/MRI/PET, bone scans, and liver imaging were only performed as clinically indicated. Physical examinations were conducted every three months during the first two years of the trial and every six months thereafter. Patients who had disease recurrence at any time were followed for survival and new relapse events annually (starting one year after the first relapse) until year 10 after randomization of the last patient. The trial protocol specified acceptable criteria for diagnosing a disease recurrence and advised histological or cytological confirmation be obtained in cases of diagnostic doubt (e.g. ill-defined, palpable mass in irradiated breast).

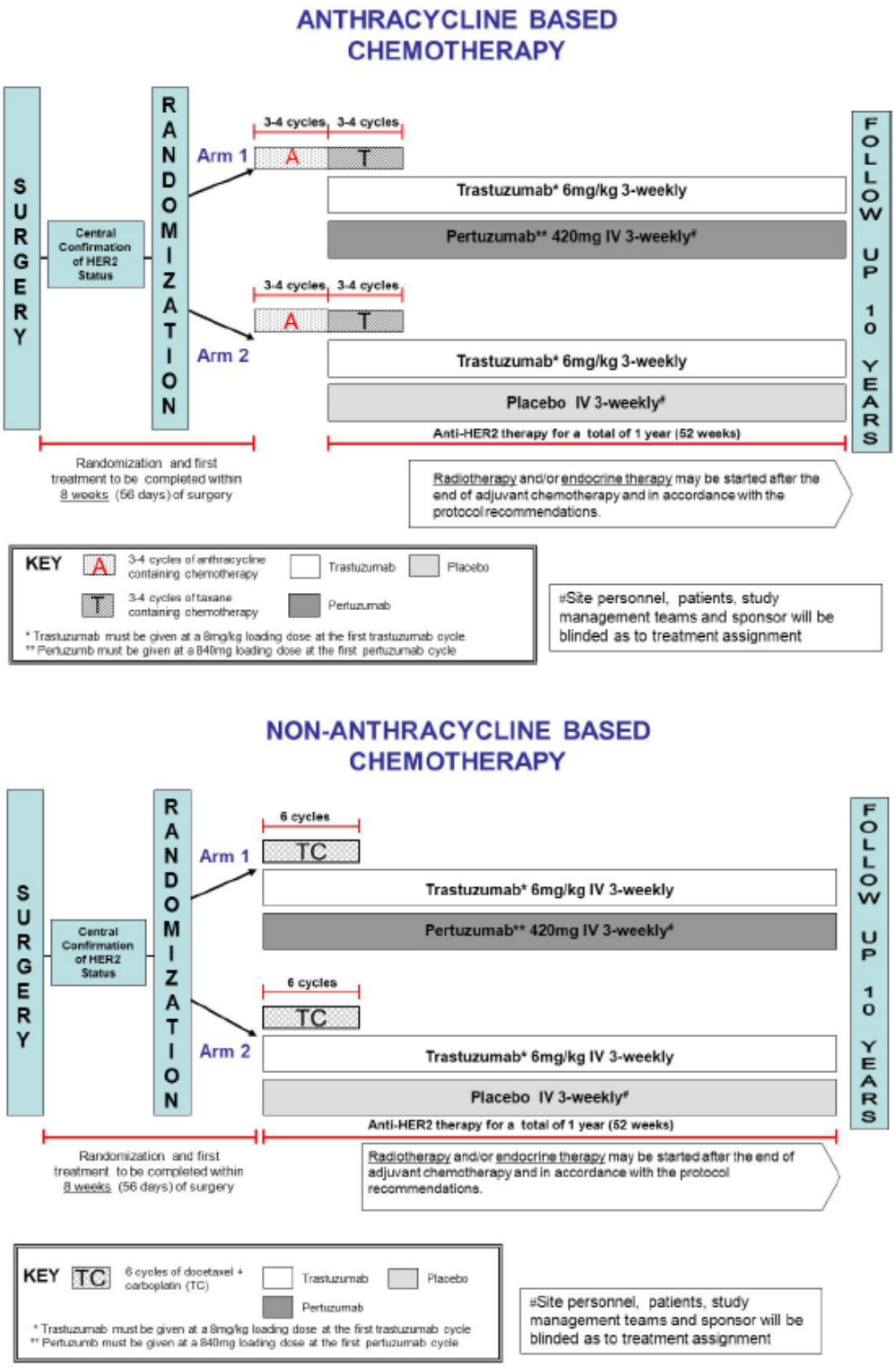


Figure 2: Study design of the APHINITY trial.

From The New England Journal of Medicine. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. 2017; 377:122-131. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Table 5: Chemotherapy regimens used in the APHINITY trial.

All study treatments will be given intravenously.
For all regimens, the maximum allowed cumulative dose of doxorubicin is 360 mg/m^2 and of epirubicin is 720 mg/m^2.
Key: A (doxorubicin), C (cyclophosphamide), E (epirubicin), F (5-fluorouracil), T (taxane)

REGIMEN	DOSE	FREQUENCY
Anthracycline therapy: FEC (or FAC) → T		
3 or 4 cycles x FEC (or FAC) → 3 or 4 cycles x docetaxel	F: 500 to 600mg/m^2 E: 90 to 120mg/m^2 or A: 50mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Docetaxel: 100mg/m^2 OR Docetaxel: 75mg/m^2 for 4 cycles[1] OR Docetaxel: 75mg/m^2 in the first cycle, escalating to 100mg/m^2 in subsequent cycles	q3w q3w q3w
3 or 4 cycles x FEC (or FAC) → 12 weekly cycles of paclitaxel	F: 500 to 600mg/m^2 E: 90 to 120mg/m^2 or A: 50mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Paclitaxel: 80mg/m^2	q1w
Anthracycline therapy: AC (or EC) → T		
4 cycles x AC[2] (or EC) → 3 or 4 cycles x docetaxel	A: 60mg/m^2 or E: 90 to 120mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Docetaxel: 100mg/m^2 OR Docetaxel: 75mg/m^2 for 4 cycles[1] OR Docetaxel: 75mg/m^2 in the first cycles, escalating to 100mg/m^2 in subsequent cycles	q3w
4 cycles x AC2 (or EC) → 12 weekly cycles of paclitaxel	A: 60mg/m^2 or E: 90 to 120mg/m^2 C: 500 to 600mg/m^2	q3w
	Followed by: Paclitaxel: 80mg/m^2	q1w
Non-Anthracycline therapy: Docetaxel/carboplatin as in BCIRG 006		
6 x docetaxel plus carboplatin	Docetaxel: 75 mg/m^2 Carboplatin: AUC 6 (900-mg maximum dose)	q3w

1 If docetaxel 75 mg/m2 is used and not escalated to 100mg/m^2, then 4 cycles must be given.
2 EC or AC can be given at the same dose (A: 60mg/m^2 or E: 90 to 120mg/m^2) every 2 weeks (dose dense) with G-CSF support, for a total of 4 cycles.

From The New England Journal of Medicine. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. 2017; 377:122-131. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Randomization, Sample Size and Statistical Analyses

Information on randomization, sample size, statistical assumptions, and other indicators of trial quality are detailed in Table 6.

Patients were randomized in a 1:1 ratio to pertuzumab-trastuzumab or placebo-trastuzumab using a centralized, permuted block randomization method that was stratified by nodal status, adjuvant chemotherapy, HR status, geographic region, and protocol version (refer to discussion below).

During the course of the APHINITY trial there were a total of three amendments to the protocol.[3] The most notable amendment (protocol version B, dated November 20, 2012) resulted in the exclusion of additional node-negative patients into the trial, an increase to the sample size, and the addition of protocol version as a stratification factor; more, specifically:

- As originally designed (protocol version A), eligible patients in the APHINITY trial included those who had either node-positive (pN ≥1; any tumour size except T0) or node-negative disease (pN0) with any tumour diameter of ≥1 cm, or a tumour diameter between 0.5 and 1 cm if at least one other high-risk factor was present (i.e., histologic or nuclear grade 3, HR-negative, or age <35 years). Trial assumptions were based on the efficacy results from BCIRG 006 trial (Slamon et al, 2011).[24] During enrollment, it was observed that the monthly recruitment rate of patients was 50% higher than expected, and the proportion of enrolled patients with node-negative disease was almost double than the proportion of these patients enrolled in BCIRG 006. Concerns that the APHINITY trial patient population would be inconsistent with BCIRG 006 led to a trial protocol amendment that stopped the recruitment of node-negative patients and increased the required sample size from 3806 to 4800 patients to include only node-positive patients. The amendment required the timing of the primary efficacy analysis to be delayed to ensure sufficient data maturity for those patients randomized after the amendment; therefore, the primary analysis would occur at 46 months. The original and revised trial assumptions are summarized in Table 5.

The required number of IDFS events and power of the APHINITY trial did not change based on the revised trial assumptions; 379 events were still required to provide 80% power to detect an HR of 0.75 at a 5%, two-sided, significance level (assuming exponential data distribution and proportional hazards). Based on BCIRG 006, a three-year IDFS rate of 89.2% was expected in the placebo group versus an assumed three-year IDFS rate of 91.8% for the pertuzumab group, which corresponds to an absolute three-year difference in IDFS of 2.6% between treatment groups.

The SAP of the trial specified that the secondary outcomes of the trial would only be tested if the primary analysis of IDFS demonstrated superiority (statistical significance) of pertuzumab-trastuzumab over placebo-trastuzumab. Secondary outcomes were tested in a specified hierarchical order to control the risk of type 1 error: IDFS (STEEP), DFS, and OS. Relapse-free interval and distant relapse-free interval were tested but not included in the adjustment for multiple testing, and therefore, should be considered exploratory endpoints. The APHINITY trial was also powered to compare OS between the treatment groups. The protocol specified three interim analyses and a final analysis of OS (Table 6); the first to occur at the time of the primary analysis and the final to occur when 640 deaths occur, which is approximately nine to 10 years after the last patient was randomized. The overall 5%, two-sided significance level for the OS analyses was controlled using O'Brien-

Fleming Lan-DeMets stopping boundaries. The final OS analysis has 80% power to detect an HR of 0.80 (p=0.0453). It was noted in the SAP that exploratory analyses of the primary outcome (IDFS in ITT population and relevant patient subgroups) would be performed at the time of the four OS analyses.

All efficacy analyses, including all secondary outcomes, were performed in the ITT population. For all time-to-event outcomes, treatment groups were compared using the log-rank test and KM methods were used to estimate three-year estimates for outcomes. All HRs and 95% confidence intervals (CIs) were estimated using a stratified Cox proportional hazard regression model.

Subgroup analyses of the primary outcome were performed by stratification and patient and disease-related factors to examine the internal consistency of the treatment effect. Tests of interaction (between treatment effect and subgroup at a 10% significance level) were also performed. These analyses were pre-specified but exploratory (uncontrolled for multiple testing), and focused on the following factors at baseline:

- Nodal status (categorized as node positive or negative, and further categorized by: 0 positive nodes and tumour ≤ 1 cm, 0 positive nodes, tumour >1 cm, 1-3 positive nodes, and ≥4 positive nodes)
- HR status (ER, PgR)
- Type of adjuvant chemotherapy (anthracycline versus non-anthracycline)
- menopausal status (pre- and post)
- Age (<40, 40-49, 50-64, ≥65)
- Type of surgery for primary tumour (breast conserving surgery versus not)
- Histological grade (grade 1, 2 or 3)
- Race (White, Black, Asian, Other)
- tumour size (<2cm, ≥2 cm - <5 cm, and ≥5 cm)
- Locoregional radiotherapy (yes/no), and).
- Female gender
- Trial protocol version (A versus B); this subgroup was added after protocol amendment B

Sensitivity analyses were preplanned to assess any imbalances between the treatment groups (number of assessments and duration of follow-up) that could influence the primary outcome results; and additional sensitivity analyses (n=10) were conducted to assess the robustness of the results to different sources of bias (patient withdrawals, start of new anti-cancer therapy, change in patient population introduced by protocol amendment B, unstratified analysis).

Patient-reported HRQOL was an exploratory outcome of APHINITY and was assessed using the EORTC QLQ-C30 and breast-specific module (BR23) questionnaires, and the EQ-5D.[1,5]

The QLQ-C30 measures overall QOL and different aspects of patient functioning. It comprises five function scales (physical, emotional, cognitive, social and role), three symptom scales (fatigue, pain, and nausea and vomiting), a global health and QOL scale, and six single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). The QLQ-BR23 consists of five multiple-item scales associated with breast cancer treatment (systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning) and three single items (sexual enjoyment, upset caused by hair loss, and future perspectives).

The EQ-5D is comprised of five questions and categorizes health states according to the following dimensions: mobility, self-care, usual activities (work, study, or leisure activities, for example), pain/discomfort and anxiety/depression, which are then used to generate an index utility score and a visual analogue scale. The scores used for determining MCIDs were not reported.

Patients completed QLQ questionnaires until disease progression or 36 months after randomization, whichever occurred first; assessment time points were pre-specified and occurred at screening, end of anthracycline treatment (if applicable), end of taxane therapy, week 25, end of HER2-targeted therapy, and 6, 12, and 24 months following the end of HER2-targeted therapy. For both instruments, a mean change from baseline of 10% or greater is considered the minimal clinically important difference (MCID). For the analysis of QOL, descriptive summary statistics for each scale score (mean, SD, 95% CI; median, IQR) and changes from baseline were calculated for each time-point by treatment group. Scales with fewer than 50% of items completed were considered missing data.

Safety assessments were performed in all patients who received at least one dose of study medication. Two specific cardiac safety endpoints were assessed in the trial, which included:

- Primary: heart failure (NYHA class III or IV) and a substantial decrease in left ventricular ejection fraction (defined as a decrease of at least 10 percentage points from baseline and to below 50%, or cardiac death
- Secondary: asymptomatic or mildly symptomatic (NYHA class II) substantial decrease in left ventricular ejection fraction as assessed by MUGA scanning or echocardiography, confirmed by a second left ventricular ejection fraction assessment (and drop) completed within three weeks.

The APHINITY trial is ongoing, and data related to the primary analysis of IDFS, secondary endpoints, and HRQOL have been published using a data cut-off of December 19, 2016.

Table 6: Select quality characteristics of the included APHINITY trial.[1]

Trial Quality Characteristics	APHINITY Trial
Treatment vs. Comparator	• Chemotherapy + trastuzumab + pertuzumab *vs.* • Chemotherapy + trastuzumab + placebo
Primary outcome	• Invasive DFS
Original required sample size (protocol version A)	• Approximately 3806 patients (379 events) were required for the trial to have 80% power to detect a hazard ratio of 0.75 at a two-sided significance level of p=0.05. The required sample size was based on the following assumptions: o A 3-year invasive DFS rate of 88% in the placebo group based on results of the BCIRG 006 trial o A 3-year invasive DFS rate of 90.9% was assumed for the pertuzumab group
Increase in required sample size (protocol version B)	• Sample size increased to 4800 patients (379 events) to address the higher than expected accrual of node-negative disease patients; after protocol version B, only node-positive patients were enrolled in order the bring the study population closer to the original trial assumptions (based on BCIRG trial) • The timing of the primary analysis was delayed until 30 months after the last patient was randomized to ensure sufficient data maturity for patients enrolled after protocol amendment B. • Revised assumptions based on new sample size: o A 3-year invasive DFS rate of 89.2% in the placebo group, which were based on results of the BCIRG 006 trial o A 3-year invasive DFS rate of 91.8% was assumed for the pertuzumab group
Randomization method	• Central web-based system; and permuted block randomization procedure stratified by: o Nodal status (0 nodes and tumour <1 cm vs. 0 positive nodes and tumour > 1 cm vs. 1-3 positive nodes vs. ≥ 4 positive nodes) o Adjuvant chemotherapy regimen (anthracycline vs. non-anthracycline) o HR status (ER and PgR negative vs. ER and/or PgR positive) o Geographic Region (USA vs. Canada/Western Europe/Australia New Zealand/South Africa vs. Eastern Europe vs. Asia-pacific vs. Latin America) o Protocol version (A vs. B)
Allocation concealment (yes/no)	• Not specified
Blinding	• Double-blind
ITT analysis (yes/no)	• Yes
Interim analyses	• Three pre-specified interim analyses and one final analysis of OS were planned with an O'Brien-Fleming α-spending function: o First interim OS analysis performed at the primary analysis of invasive DFS (379 invasive DFS events, 26% information fraction; p<0.00001) o Second interim OS analysis (49% information fraction; p=0.0027) o Third interim OS analysis (70% information fraction; p=0.0139) o Final OS analysis (640 events, 100% information fraction; p=0.0453)
Final analysis (yes/no)	• No • Final analysis of OS expected in 2023, approximately 10 years after the last patient was randomized to the study
Early termination (yes/no)	• No
Ethics approval (yes/no)	• Yes

Abbreviations: BCIRG - Breast Cancer International Research Group; DFS - disease-free survival; ER - estrogen receptor; HR - hormone receptor; ITT - intent-to-treat; OS - overall survival; PgR - progesterone receptor; vs. versus.

Populations

Patient randomization occurred between November 2011 and August, 2013. During that period a total of 4805 patients were randomized to receive chemotherapy and trastuzumab plus either pertuzumab (n=2400) or placebo (n=2405). Overall, the baseline characteristics of patients were well balanced between the two treatment groups (Table 7). Most randomized patients were treated at trial sites in the geographic categories of Canada/Western Europe/Australia/New Zealand/South Africa (54%) and Asia-Pacific (23%).[3] The median age of patients was 51 years, with 13% of patients aged 65 and older.[3] All patients had centrally confirmed HER2-positive tumours and an ECOG performance status of 0 or 1. The majority of patients had HR-positive (64%; 36% HR-negative) and node-positive disease (63%). Of the 37% (n=1799) of patients with node-negative disease, 3.6% (n=174) and 33.8% (n=1625) had tumour sizes of ≤1 cm and >1cm, respectively. When the entire trial population is considered, approximately 6% of patients had tumours <1 cm in size.[4] The trial enrolled 11(<1%) male patients. Most patients in the trial were randomized into the trial under protocol version A (76%). A comparison of baseline characteristics between patients enrolled under protocol version A versus B indicated that a higher proportion of patients enrolled under protocol B were Asian, underwent mastectomy, and had larger tumour size. These differences (apart from Asian race) are expected based on inclusion of only node-positive patients after the protocol B amendment.[3]

Table 7: Baseline patient and disease characteristics of patients in the APHINITY trial.

	Pertuzumab + trastuzumab + chemotherapy N = 2400	Placebo + trastuzumab + chemotherapy N = 2404
Nodal status – no. (%)	n = 2400	n = 2404
0 positive nodes and tumor ≤1 cm*	90 (3.8)	84 (3.5)
0 positive nodes and tumor >1 cm*	807 (33.6)	818 (34.0)
1–3 positive nodes	907 (37.8)	900 (37.4)
≥4 positive nodes	596 (24.8)	602 (25.0)
Adjuvant chemotherapy regimen (randomized) – no. (%)	n = 2400	n = 2404
Anthracycline-containing regimen	1865 (77.7)	1877 (78.1)
Non-anthracycline-containing regimen	535 (22.3)	527 (21.9)
Hormone receptor status (central) – no. (%)	n = 2400	n = 2404
Negative (ER- and PgR-negative)	864 (36.0)	858 (35.7)
Positive (ER- and/or PgR-positive)	1536 (64.0)	1546 (64.3)
Protocol version – no. (%)	n = 2400	n = 2404
Protocol A	1828 (76.2)	1827 (76.0)
Protocol Amendment B	572 (23.8)	577 (24.0)
Age – yr	n = 2400	n = 2404

Mean (SD)	51.7 (10.9)	51.4 (10.7)
Median	51.0	51.0
Range	22–86	18–85
Age – yr – no. (%)	n = 2400	n = 2404
<35	149 (6.2)	144 (6.0)
35–39	177 (7.4)	183 (7.6)
40–49	708 (29.5)	702 (29.2)
50–64	1051 (43.8)	1082 (45.0)
65–74	285 (11.9)	267 (11.1)
≥75	30 (1.3)	26 (1.1)
Sex – no. (%)	n = 2400	n = 2404
Female	2397 (99.9)	2396 (99.7)
Male	3 (0.1)	8 (0.3)
Menopausal status at screening – no. (%)	n = 2397	n = 2395
Pre-menopausal	1152 (48.1)	1173 (49.0)
Post-menopausal	1242 (51.8)	1220 (50.9)
Unknown	3 (0.1)	2 (<0.1)
Pathologic tumor size – cm	n = 2400 tumors	n = 2405 tumors
Mean (SD)	2.4 (1.5)	2.5 (1.5)
Median	2	2
Range	0–18	0–14

Pathologic tumor size – cm – no. (%)	n = 2400 tumors	n = 2405 tumors
0–<2	978 (40.8)	948 (39.4)
≥2–<5	1275 (53.1)	1283 (53.3)
≥5	147 (6.1)	174 (7.2)

* Protocol A only.

Patients with bilateral tumors will report pathologic characteristics for both tumors; therefore, pathologic tumor characteristics are summarized on the tumor level.

ER denotes estrogen receptor, PgR progesterone receptor, and SD standard deviation.

From The New England Journal of Medicine. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. 2017; 377:122-131. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

b) Interventions

Patients in the APHINITY trial were randomized to receive either pertuzumab or placebo (840 mg intravenously as a loading dose, followed by 420 mg intravenously every three weeks) combined with trastuzumab (8 mg intravenously per kg of body weight as a loading dose, followed by 6 mg per kg every three weeks), beginning at the first cycle of taxane chemotherapy and continuing for a maximum of 18 treatment cycles (one year). As previously mentioned, choice of permitted adjuvant chemotherapy (6 to 8 cycles) was at the discretion of treating investigators and could be anthracycline or non-anthracycline-based. Details on the chemotherapy regimens used in the trial are summarized available in (Table 5).

Dose Delays/Interruptions and Modifications

Dose delays/interruptions were permitted in the trial to assess and/or manage toxicities associated with treatment, however patients were withdrawn from study if dose delays of targeted agents exceeded more than two treatment cycles. Dose modifications were not permitted for either targeted agent but were allowed for chemotherapy according to specified guidelines in the trial protocol. Patients discontinuing chemotherapy due to toxicity could continue in the trial and receive targeted therapy. Dose delays or interruptions due to AEs were required in approximately half of patients in both treatment groups; 51.1% of patients in the pertuzumab-trastuzumab group and 50.4% of patients in the placebo-trastuzumab group.[3]

Duration of Treatment

At the time of the primary analysis, 84.5% of patients in the pertuzumab-trastuzumab treatment group and 87.4% of patients in the placebo-trastuzumab group had completed study treatment. The median duration of study treatment (chemotherapy and targeted therapy) and targeted therapy were the same in both groups at 64 weeks and 55 weeks, respectively[3]. The median cumulative dose of pertuzumab received by patients in the pertuzumab-trastuzumab group was 7980 mg (range, 420-9660 mg).[3]

Concomitant Treatments and Medications

The trial protocol specified HT and RT be given at the end of chemotherapy while targeted treatment was being administered. A similar majority of patients in each treatment group received adjuvant RT; 72.8% in the pertuzumab-trastuzumab group and 72.2% in the placebo-trastuzumab group; while the majority of HR-positive patients in each treatment group received adjuvant hormonal therapy (87.3%, n=1317/1508 in the pertuzumab-trastuzumab group; 85.8%, n=1330/1551 in the placebo-trastuzumab group).[3] The most common type of HT received by patients in both groups were SERMs (approximately 44% in both groups) and AIs (29.2% in the pertuzumab-trastuzumab group versus 26.6% in the placebo-trastuzumab group).[3]

Nearly all patients in the trial received at least one concomitant medication on study (approximately 94% in each treatment group); the medications received were primarily 5-HT3 antagonists and corticosteroids (>80% of patients received both medications in each treatment group), which are not unexpected with anthracycline/taxane-based chemotherapy.[2]

c) Patient Disposition

The disposition of patients through the APHINITY trial is summarized in Table 8.

Of the 6263 patients screened for the trial, a total of 4805 were randomized. The most common cause of screen failure was lack of HER2-positivity by central laboratory, which accounted for approximately half of screen failures.[3] There were 22 patients (<0.1%) and 13 patients (<0.1%) in the pertuzumab-trastuzumab and placebo-trastuzumab groups, respectively, who did not receive their assigned study treatment; this was primarily due to patient decision to withdrawal from the study.[29] There were 62 (1.3%) patients who received non-randomized study drug in error; 38 (1.6%) patients in the pertuzumab-trastuzumab group received chemotherapy without pertuzumab, and 24 (<0.1%) patients in the placebo-trastuzumab group received pertuzumab.[3] At the data cut-off date, most patients had completed allocated study treatment; among patients discontinuing treatment (15.5% in the pertuzumab group versus 12.6 in the placebo group), the main reasons for treatment discontinuation in both groups were AEs and non-safety reasons that included non-compliance with study drug and withdrawal by subject. Almost all randomized patients entered trial follow-up (approximately 99% of patients in each group), however, a similar proportion of patients in each group (15.4%, n=370 in the pertuzumab group and 16.6%, n=399 in the placebo group) had discontinued by the data cut-off date. [3] The primary reasons for discontinuing follow-up in both groups was disease recurrence and patient decision to withdrawal. At the time of the primary analysis, approximately 90% of patients remained alive and on study in both treatment groups.[3]

The ITT primary analysis population is comprised of 4804 patients, and not the 4805 patients originally randomized; one patient in the placebo-trastuzumab group was excluded after randomization on the basis of falsification of personal information.

Major protocol deviations occurred in approximately 28% of patients in each treatment group during the trial; the distributions and types of deviations, which primarily related to inclusion/exclusion criteria and study procedures and assessments, were very similar between groups.[3] The most frequent deviations included the time interval between breast cancer surgery and randomization being

outside the specified time period of 8 weeks; inability to start treatment within one week of randomization; completion of all necessary baseline investigations; abnormal laboratory results immediately prior to randomization. The equal distribution of deviations between the groups makes it unlikely that deviations influenced the efficacy results of the trial.[3]

Table 8: Patient disposition in the APHINITY trial.[3]

Patient Disposition, N (%)	Pertuzumab-Trastuzumab	Placebo-Trastuzumab
Screened	6263	
Randomized total	4805[a]	
Randomized per group	2400	2404
Received allocated study drug	2364 (98.5)	2405 (100)
Did not receive study drug	22 (<0.1)	13 (<0.1)
allocated to pertuzumab but received chemotherapy only	38 (1.6)	-
allocated to placebo but received pertuzumab	-	24 (<1.0)
Completed allocated study treatment	2028 (84.5)	2100 (87.4)
Discontinued allocated study treatment	372 (15.5)	304 (12.6)
Safety reasons:	186 (7.8)	155 (6.4)
AE	176 (7.3)	149 (6.2)
Death	9 (0.4)	6 (0.2)
Pregnancy	1 (<0.1)	0
Non-safety reasons:	186 (7.8)	149 (6.2)
Lost to follow-up	0	1 (<0.1)
Non-compliance with study drug	44 (1.8)	29 (1.2)
Physician decision	30 (1.3)	15 (0.6)
Protocol violation	1 (<0.1)	3 (0.1)
Recurrence of disease	20 (0.8)	29 (1.2)
Contralateral breast cancer	2 (<0.1)	0
Withdrawal by subject	55 (2.3)	47 (2.0)
Other	34 (1.4)	25 (1.0)
Entered Follow-up	2368 (98.7)	2381 (99.0)
Discontinued follow-up at DCOD (December 19, 2016)	370 (15.4)	399 (16.6)
Reasons		
AE	10 (0.4)	16 (0.7)
Death	17 (0.7)	17 (0.7)
Lost to follow-up	19 (0.8)	20 (0.8)
Physician decision	10 (0.4)	9 (0.3)
Recurrence of disease	132 (5.5)	171 (7.1)
Contralateral breast cancer	5 (0.2)	11 (0.5)
Withdrawal by subject	163 (6.8)	148 (6.2)
Other	14 (0.6)	8 (0.3)
Status at DCOD:		
Alive and remain in study	2178 (90.8)	2186 (90.9)
Dead	80 (3.3)	89 (3.7)
No longer in study	142 (5.9)	129 (5.4)
Analysis populations:		
ITT	2400	2404
Safety	2364	2405

Abbreviations: DCOD - data cut-off date.

Notes:
[a] - one patient was excluded from the ITT population due to falsification of personal information.

d) Critical Appraisal and Limitations

Critical appraisal of the APHINITY trial was based on the primary trial publication, additional data published in posters presented at ASCO 2018, a recent assessment report by EMA, as well as unpublished data provided to pCODR by the Manufacturer. Overall, the trial was of good quality. The randomization procedure was carried out appropriately although details of allocation concealment were not reported. The treatment groups were well balanced at baseline for important patient and prognostic characteristics, and length of time on treatment was the same in both treatment groups. There was also transparent reporting of the disposition of patients through the trial; reasons for treatment and follow-up discontinuation were balanced between the treatment groups, and all efficacy analyses were performed according to the ITT principle. Notwithstanding the quality of the trial, a number of limitations were noted, and areas of uncertainty identified, which are important when interpreting the results of the APHINITY trial, and include the following:

- The primary outcome of the trial, IDFS, which is a composite endpoint, has not been validated in the published literature. Therefore, the strength of association between this surrogate definition and OS is unknown. Further, use of a modified, non-standard definition introduces challenges related to analysis and interpretation when making cross-trial comparisons. Unlike the STEEP definition of IDFS, which is commonly used in adjuvant breast cancer trials, the definition used in APHINITY did not include second primary invasive non-breast cancer as an event. Consequently, it likely provides a more conservative estimate of treatment effect compared to the other DFS endpoints assessed in the trial (which included the STEEP definition). Since the primary outcome was consistent with these other DFS endpoints, which included standard definitions, the pCODR Methods Team considered its use acceptable.
- Protocol amendment B, which stopped the enrolment of further node-negative patients into the trial (thereby increasing the proportion of node-positive patients into the trial) and increased the sample size from 3806 to 4804 patients, changed the composition of patients in the trial, and as a result, there is a possibility that APHINITY may not be entirely representative of all patients with HER2-positive breast cancer. It is also unclear how the sample size increase affected the power of the trial. It is possible that the trial may have been overpowered, as it detected an absolute difference in IDFS at three years between the groups that was smaller (0.9%) than what was specified as the clinically important difference in the amended SAP (2.6%). Larger sample size is associated with increased statistical power; as sample size and power increase, progressively smaller differences between treatment groups in the primary outcome will be identified as statistically significant.[7] However, differences between treatment groups identified as statistically significant may not be clinically significant. The clinical significance of the treatment benefit observed with pertuzumab combination treatment in APHINITY is questionable.
- At the primary analysis, the APHINITY trial demonstrated a statistically significant difference in IDFS in favour of pertuzumab-trastuzumab. The stratified HR in the ITT population was 0.81 (0.66-1.00; p=0.045), suggesting a 19% reduction in the risk of invasive disease events (absolute

difference of 0.9% in IDFS at three years). However, the upper confidence limit was the null value of 1.00, which indicates there is insufficient evidence to conclude that the groups were indeed statistically significantly different.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter suggesting that it is incorrect to refer to the observed statistical difference as being "marginal," as the reported p-value was less than 0.05 (and the upper limit of the confidence interval for the hazard ratio (HR) was exactly 0.995). pERC discussed the response provided by the pCODR Methods Lead in the pCODR Clinical Guidance Report and agreed the difference was statistically significant. Furthermore, pERC noted that the results of the primary analysis are cited as they appear in the primary trial publication (HR for IDFS = 0.81; 95% CI, 0.66 to 1.00; P = 0.045); therefore, no change is required in the style used for reporting of the confidence interval.

- The KM curves for the primary outcome (including curves for subgroups analyses by nodal status) suggest that the proportional hazards assumption for the analysis may have been violated; the curves continuously overlap until about 20 months, after which point the curves separate and show a very slight treatment benefit in favour of pertuzumab. For this reason, the HR estimates reported in the trial should be interpreted with caution. The KM curves for IDFS (STEEP) were similar to the primary IDFS outcome.
- The Submitter's Health Canada indication and pCODR funding request is focused on patients with HER2-positive breast cancer at high-risk of recurrence, which they have defined by the presence of either node-positive disease or HR-negative disease. The evidence informing this request is from subgroup analysis results of the trial. The pCODR Methods Team disagrees with the Submitter that the evidence from these analyses clearly demonstrate treatment with pertuzumab is more efficacious in these particular patients; specifically:
    - The subgroups analyses were pre-specified but exploratory, and therefore not desinged to test for differences in treatment effect among categories of patient subgroups. The analyses were also not adjusted for multiplicity (type 1 error); 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 APHINITY trial numerous analyses (secondary, subgroup, and sensitivity) were performed.
    - The treatment effect estimate obtained for the node-positive patient subgroup was HR=0.77 (95% CI, 0.62-0.96), and for the HR-negative subgroup was HR=0.76 (95% CI, 0.56-1.04); the absolute difference between groups in three-year IDFS was 1.8% and 1.6%, respectively. Upon closer examination of the events in the HR-negative subgroup, it appears the trend observed in this subgroup is likely driven by the high proportion of node-positive patients in this group.[6] The treatment effect size obtained for another patient subgroup, tumour size <2 cm (HR=0.62; 95% CI, 0.42-0.92), was actually of greater magnitude than that observed for node-positive patients, but this patient group was not discussed in the Submitter's definition of high-risk of recurrence. It seems reasonable that

tumour size would be of similar prognostic importance as nodal or HR status. The Submitter's rationale for selecting patients at high-risk for recurrence (HR-negative status and not tumour size) is unclear to the pCODR Methods Team; and does not align with the subgroup analysis results of the trial.

    - The statistical tests for interaction were non-significant for all but one subgroup analysis (menopausal status), which suggests that all patient factors examined, including nodal and HR status, were not associated with a statistically significant difference in treatment effect. Therefore, there is little evidence of heterogeneity of treatment effect between the patient subgroups.
    - The efficacy of pertuzumab in node-negative patients should be considered unclear based on the APHINITY trial data. The amendment change that reduced the number of these patients in the trial and the low event rate (n=32 in the pertuzumab group versus n=29 in placebo group) precludes any conclusions on efficacy.

- Ten pre-specified sensitivity analyses were performed to assess the robustness of the primary outcome results.[3] Results from half (five) of these analyses did not align with the primary analysis results (were not statistically significant), and included the following analyses:
    - Counted patients as having an IDFS event at the time of new anti-cancer therapy (if date of receiving new anti-cancer therapy was prior to first IDFS event)
    - Patients who discontinued follow-up without a recurrence were considered to have a recurrence at the next planned assessment (if they had continued in the study)
    - Counted patients who withdrew from targeted treatment due to AEs as having an IDFS event (one day after the date last known to be recurrence free)
    - Counted patients who discontinued study follow-up as having an IDFS event (one day after the date last known to be recurrence free)
    - Unstratified analysis
- APHINITY was an international trial; consequently, differences in RT and HT standard practices by geographic region, in additional to the use of different chemotherapy regimens, may have added heterogeneity in testing for treatment effect.

In their feedback on the initial recommendation, the submitter disagreed with pERC's statement that the Committee is not satisfied that there is a clinically meaningful net clinical benefit of pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy. Specifically the submitter argued that:

(1) There is a clinically meaningful net clinical benefit of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive early breast cancer at high risk of recurrence. APHINITY was the largest international, multi-centre, phase III double-blind, placebo-controlled

randomised study conducted of pertuzumab + trastuzumab + chemotherapy as adjuvant treatment in almost 5,000 HER2-positive early breast cancer patients. This study's primary analysis was the first to improve upon the high bar set by the current standard of care in this curative setting and to demonstrate statistically significant superiority in IDFS over placebo + trastuzumab + chemotherapy in the intention-to-treat population (ITT) (IDFS RR = 0.813; 95% CI, 0.664 to 0.995; P = 0.0446; two-sided alpha = 5%).

In response to the submitter's feedback the pCODR Methods lead reiterated that a protocol amendment increased the sample size of the APHINITY trial by approximately 1000 patients. While it is unclear how this significant increase in sample size affected the power of the trial, it is quite possible that APHINITY was overpowered, as it detected an absolute difference in IDFS between treatment groups at three years of 0.9%, which is smaller than the 2.6% difference that was pre-specified as clinically significant in the SAP. The Methods Team maintains that the clinical significance of the 0.9% absolute difference in IDFS between the treatment groups in the APHINITY trial remains questionable.

(2) There is a clinically meaningful net clinical benefit of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive early breast cancer node-positive disease. In a situation where the ITT analysis is positive, it is appropriate to investigate the consistency of the primary analysis results across pre-specified subgroups. In early breast cancer, including HER2-positive breast cancer, lymph node involvement is associated with poor prognosis. Patients in this pre-defined subgroup derived even greater benefit from the addition of pertuzumab with an IDFS hazard ratio estimate that was lower than in the overall ITT population. On average, patients in this large lymph node positive subgroup (N=3,005) derived a 23% reduction in the risk of recurrence or death (IDFS HR = 0.768; 95% CI, 0.616 to 0.958).

In response to the submitter's feedback the pCODR Methods lead agreed that in trials where the ITT analysis for the primary outcome is statistically significant, it is appropriate to investigate the consistency of the results in pre-specified subgroups of patients. However, it should be acknowledged that in most trials, including APHINITY, subgroup analyses are exploratory in nature, and therefore should be considered hypothesis-generating since they are not designed to test for differences in treatment effect among categories of patients within a subgroup. Further, the subgroup analyses in APHINITY were not controlled for multiple testing (which increases the risk of type 1 error; claiming a difference when one does not truly exist), and tests for statistical interaction were non-significant for every subgroup examined with the exception of menopausal status, which provides little evidence of heterogeneity of treatment effect. Therefore, based on the identified limitations and the results obtained, the Methods Team maintains that the subgroup analyses do not clearly demonstrate that the combination of pertuzumab-trastuzumab is more efficacious in lymph node positive patients.

- HRQOL was an exploratory endpoint of the APHINITY trial, and as such, the results of the QOL assessment should be interpreted as descriptive. Caution is advised in making inferences based on the reported treatment comparisons considering that, for most QOL scales, it was not indicated whether mean scores in the treatment groups were similar at baseline. The QOL data are further limited by selective reporting; numerical or

descriptive data (graphs or figures) were not presented for a number of QLQ-C30 scales (cognitive, social and emotional functioning; majority of symptom scales) and for all BR23 scales.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The efficacy outcomes of the APHINITY trial are summarized in Table 9. The primary analysis is based on a data cut-off date of December 19th, 2016, at which time the median follow-up of patients in the trial was 45.4 months (3.78 years).[1]

Primary Outcome: Invasive DFS

The primary analysis took place when 381 IDFS events were observed; there were 171 (7.1%) IDFS events in the pertuzumab group compared to 210 (8.7%) events in the placebo group. APHINITY met its primary outcome demonstrating a statistically significant improvement in IDFS in the pertuzumab treatment group (HR=0.81, 95% CI, 0.66-1.00; p=0.045. Figure 3A). The three-year rates of IDFS were 94.1% in the pertuzumab group and 93.2% in the placebo group (absolute difference of 0.9%). Distant recurrences were the most frequent first invasive disease-free event to occur in both treatment groups; 4.7% (n=112) in the pertuzumab group and 5.8% (n=139) in the placebo group; and these distant metastases were in the CNS in approximately 1.9% and 1.8% of patients, respectively (Table 9). CNS or visceral metastases (lung, liver) were more common than bone as the first site of metastases.

Patient subgroup analyses for IDFS are summarized in Figure 4. Most subgroup analyses demonstrated a treatment effect that favoured treatment with pertuzumab-trastuzumab, with the exception of patients with node-negative disease (HR=1.13, 95% CI, 0.68-1.86; Figure 3B), which favoured treatment with placebo. The greatest magnitude of treatment benefit with pertuzumab was in patients who were post-menopausal (HR=0.68, 95% CI, 0.51-0.91), had node-positive disease (HR=0.77, 95% CI, 0.62-0.96; Figure 3C), and tumour size less than 2 cm (HR=0.62, 95% CI, 0.42-0.92); however, tests for interaction for these subgroups were non-significant, suggesting the treatment effect was not significantly different among the categories of patients in these subgroups.

Since a statistically significant result was obtained for the primary outcome of the trial, the secondary outcomes of the trial were tested sequentially (as described in section 6.3.2.1) in the following order: IDFS (STEEP), DFS, and OS.

IDFS (STEEP) and DFS

The alternate definitions of DFS evaluated in the trial were consistent with the primary outcome results (Table 9). IDFS by STEEP definition, which includes second primary invasive non-breast cancers (HR=0.82, 95% CI, 0.68-0.99; p=0.043), and DFS, which includes second primary invasive non-breast cancers and non-invasive breast cancers (HR=0.81, 95% CI, 0.67-0.98; p=0.033), produced treatment effect estimates of similar magnitude to the primary outcome definition of IDFS.

Overall Survival

At the primary analysis cut-off date, a total of 169 patients had died; 80 (3.3%) in the pertuzumab-trastuzumab group and 89 (3.7%) in the placebo-trastuzumab group. The first interim analysis of OS data did not demonstrate a significant difference in mortality between the treatment groups (HR=0.89; 95% CI, 0.66-1.21; p=0.47). The OS data are currently immature with an information fraction of 26%.[3]

Relapse-free Interval and Distant Relapse-free Interval

Relapse-free interval and distant-relapse free interval were not included in the adjustment for multiple testing of secondary outcomes. The results for these endpoints are available in Table 9, and show treatment effect estimates consistent with IDFS and DFS outcomes; however, for distant-relapse-free survival the difference in event rates between the groups was not statistically significant.

Table 9: Efficacy outcomes in the APHINITY trial.[1]

Efficacy Outcomes	Trastuzumab + Pertuzumab (n=2400)	Trastuzumab + Placebo (n=2404)
Data cut-off date	December 19, 2016	
Median follow-up, months	45.4	
Primary outcome		
Invasive DFS[a]		
No. events (%)	171 (7.1)	210 (8.7)
Category of first invasive DFS event:[b]		
Distant recurrence	112 (4.7)	139 (5.8)
CNS metastases	45 (1.9)	44 (1.8)
Locoregional recurrence	26 (1.1)	34 (1.4)
Contralateral breast cancer	5 (0.2)	11 (0.5)
Death without previous event	28 (1.2)	26 (1.1)
3-year event-free rate, %	94.1	93.2
Hazard ratio (95% CI); p-value	0.81 (0.66-1.00); p=0.045	
Secondary outcomes		
Invasive DFS - STEEP Definition[c]		
No. events (%)	189 (7.9)	230 (9.6)
3-year event-free rate, %	93.5	92.5
Hazard ratio (95% CI); p-value	0.82 (0.68-0.99); p=0.043	
DFS[d]		
No. of events (%)	192 (8.0)	236 (9.8)
3-year event-free rate, %	93.4	92.3
Hazard ratio (95% CI); p-value	0.81 (0.67-0.98); p=0.033	
Relapse-free interval[e]		
No. of events (%)	138 (5.8)	173 (7.2)
3-year event-free rate, %	95.2	94.3
Hazard ratio (95% CI); p-value	0.79 (0.63-0.99); p=0.043	
Distant relapse-free interval[f]		
No. of events (%)	119 (5.0)	145 (6.0)
3-year event-free rate, %	95.7	95.1
Hazard ratio (95% CI); p-value	0.82 (0.64-1.04); p=0.101	
OS		
No. of events (%)	80 (3.3)	89 (3.7)
Hazard ratio (95% CI); p-value	0.89 (0.66-1.21); p=0.47	

Abbreviations: CI confidence interval; CNS - central nervous system; DFS - disease-free survival; OS - overall survival.

Notes:
[a] - Invasive DFS was defined as the time from randomization until the date of the first occurrence of one of the following events: ipsilateral invasive breast tumour recurrence, recurrence of ipsilateral locoregional invasive disease, a distant recurrence, contralateral invasive breast cancer, or death from any cause. This definition excludes second primary non-breast cancer as an invasive disease event.
[b] - Patients who had an additional invasive-disease event within 61 days of their first event are reported in the category according to the following hierarchy: distance recurrence, locoregional recurrence, contralateral breast cancer, and death without a previous event.

[c] - Invasive DFS - STEEP Definition - is defined the same way as the primary outcome of invasive DFS but the STEEP definition includes second primary non-breast cancers (with the exception of non-melanoma skin cancers and in situ carcinoma of any site).
[d] - DFS was defined as the time between randomization and the date of first occurrence of an invasive disease-free survival event including a second primary non-breast cancer event or contralateral or ipsilateral DCIS.
[e] - Relapse-free interval was defined as the time between randomization and the date of local, regional or distant breast cancer recurrence.
[f] - Distance relapse-free interval was defined as the time between randomization and the date of distant breast cancer recurrence.
* Hazard ratios < 1.00 favour treatment with pertuzumab.

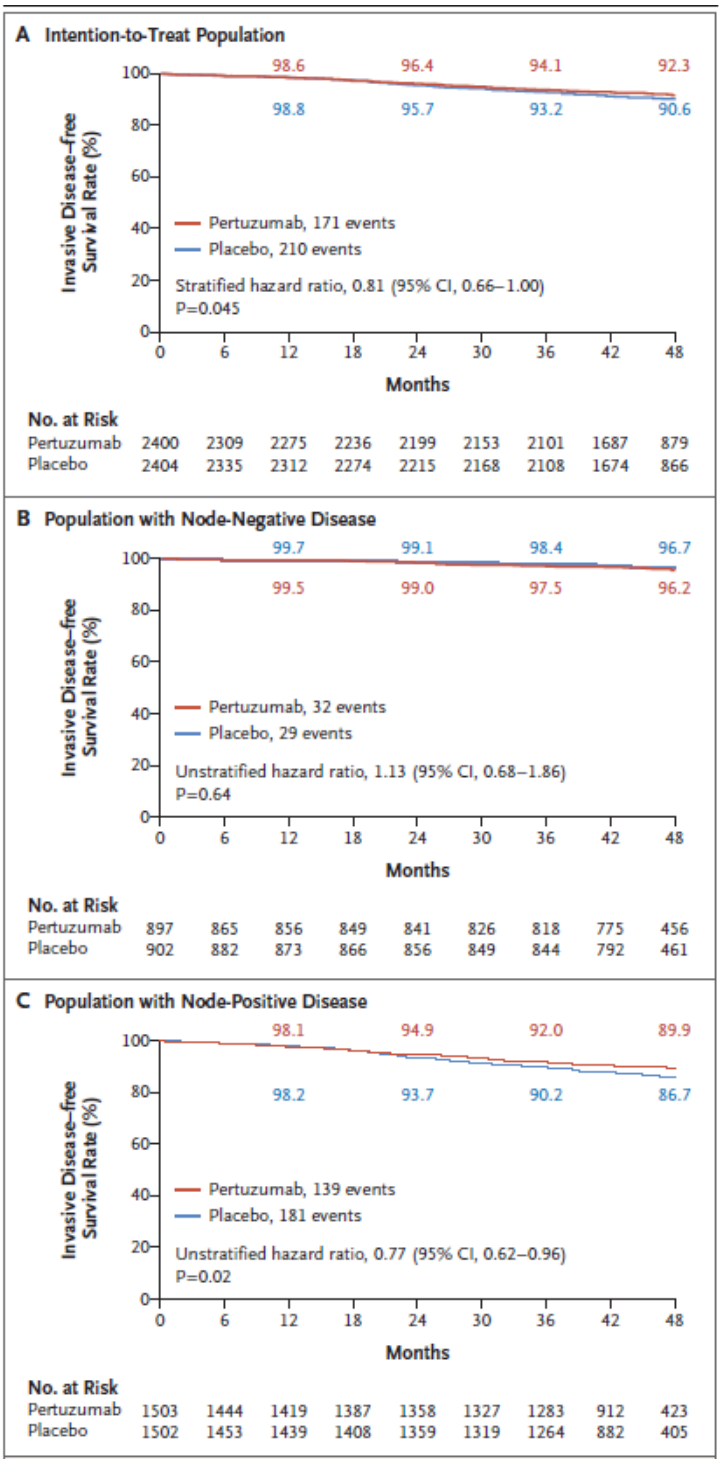


Figure 3: Kaplan Meier curves for the primary outcome of invasive DFS in (A) ITT patient population, (B) subgroup of patients with node-negative disease at baseline, and (C) subgroup of patients with node-positive disease at baseline in the APHINITY trial.

From The New England Journal of Medicine. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. 2017; 377:122-131. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

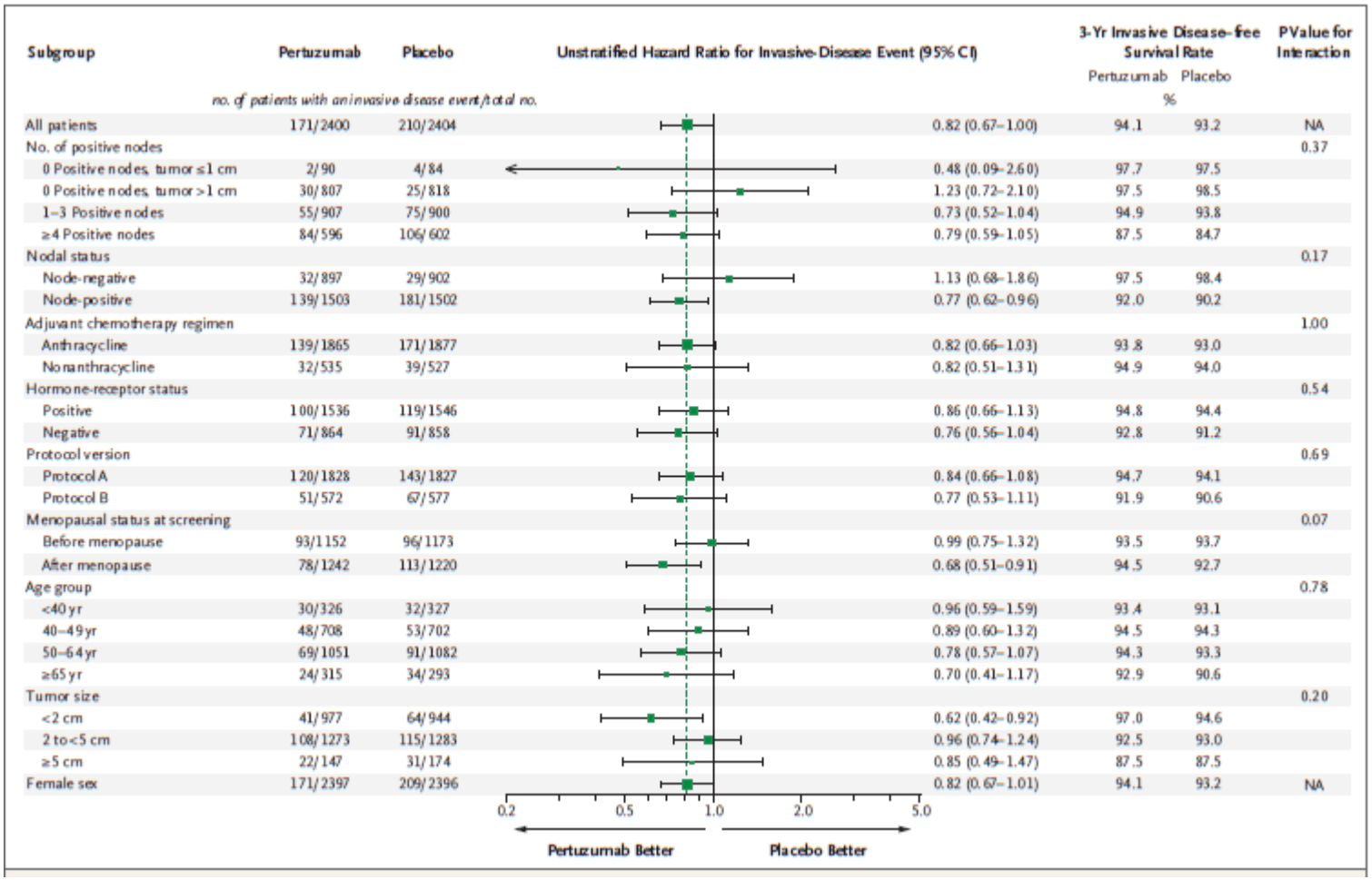


Figure 4: Patient subgroup analyses for the primary outcome of invasive DFS in the APHINITY trial.

From The New England Journal of Medicine. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. 2017; 377:122-131. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Quality of Life

Some HRQOL data were reported in the APHINIITY trial publication,[1] but more recently, data were presented in a conference poster at ASCO in June 2018.[5] EQ-5D data were not reported in either of these sources, but were found in the EMA report.[3]

EORTC QLQ questionnaire completion rates were reported as consistently high throughout the trial, with at least 87% of patients remaining on study at each assessment time point and completing at least one question (in each treatment group). There were no notable differences in completion rates between the treatment groups nor between patients treated with anthracycline-based versus non-anthracycline-based chemotherapy. Other than for functional scales, neither data source reported whether mean scores at baseline were similar between the treatment groups for the other QLQ-C30 and B23 scales. Reporting of QOL was further limited by provision of mostly narrative summaries of QOL data; numerical or descriptive data (graphs or figures) were not presented for a significant number of scales (cognitive, social and emotional functioning, and a majority of symptom scales for the QLQ-C30; all scales for BR23).

Patients in both treatment groups reported a clinically meaningful decline in mean global health status scores from baseline to the end of taxane chemotherapy (−11.2 [95% CI, −12.2 to −10.2] and −10.2 [95% CI, −11.1 to −9.2] in the pertuzumab and placebo groups, respectively), with scores returning to baseline during targeted treatment (Figure 5). No significant difference in mean scores was observed between the groups.

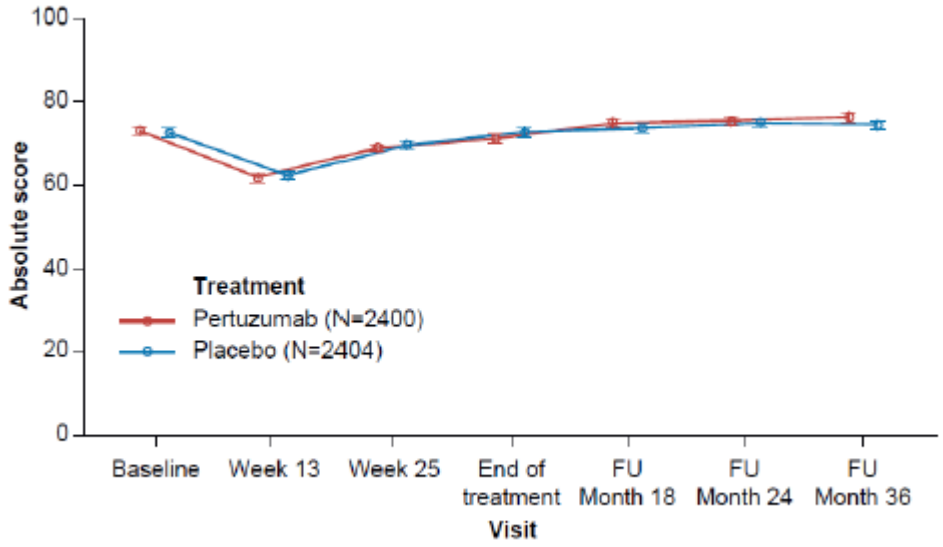


Figure 5: Mean QLQ-C30 Global Health Status scores over time by treatment group.

From The New England Journal of Medicine. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. 2017; 377:122-131. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

In terms of patient functioning, mean scores in physical, cognitive, role, social, and emotional functioning scales were comparable between the treatment groups over time, and no clinically meaningful declines in mean scores were observed between the treatment groups for any scale except for physical functioning. Physical functioning scores declined from baseline until the end of taxane chemotherapy but returned to baseline during targeted therapy. Mean physical function scores were -10.7 (95% CI, -11.4 to -10.0) and -10.6 (-11.4 to -9.9) in the pertuzumab and placebo groups, respectively.

In terms of symptoms, the scales for fatigue, dyspnea, and appetite loss reportedly all showed clinically meaningful worsening in mean scores from baseline to the end of taxane chemotherapy in both treatment groups; however, no differences in mean scores between groups were observed. Patients in both treatment groups reported worsening in diarrhea symptoms over time that persisted until the end of taxane chemotherapy; the mean change in score from baseline was 29.8 (95% CI, 21.0 to 23.6) in the pertuzumab group and 9.2 (95% CI, 8.2 to 10.2) in the placebo group. While scores in both groups improved over time they remained elevated during HER2-targeted treatment, and the deterioration was clinically meaningful in the pertuzumab group but not in the placebo group (Figure 6).

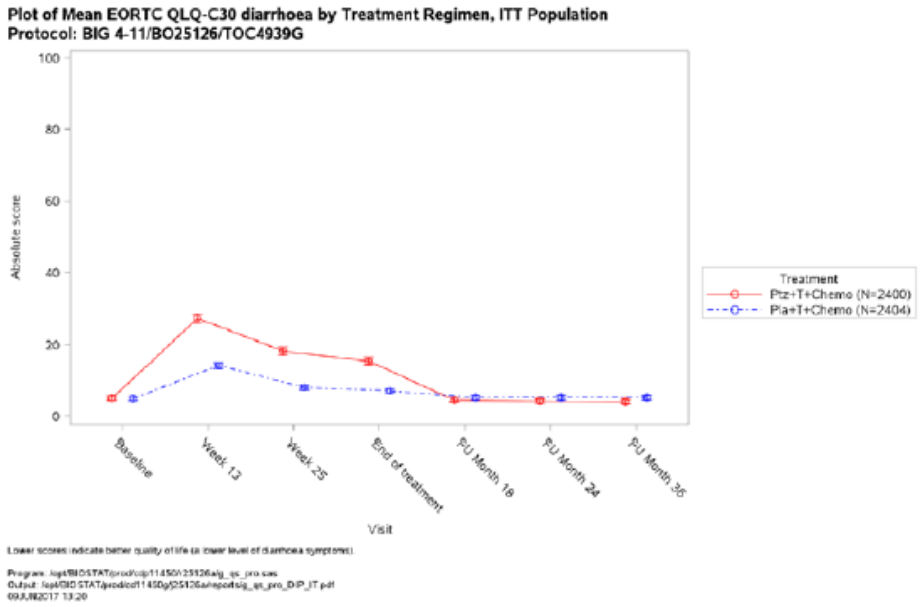


Figure 6: Mean patient-reported QLQ-C30 diarrhea symptoms by treatment group.[3]

Other symptom scores, including financial difficulties, insomnia, nausea and vomiting, constipation, and pain showed no clinically meaningful changes in mean scores from baseline during the trial.

For the EORTC-QLQ-BR23, mean scores for body image and systemic chemotherapy side effects worsened from baseline to the end of taxane chemotherapy in both treatment groups but returned to baseline during targeted therapy; no clinically meaningful differences in mean scores were observed between the groups. Approximately 300 patients in each treatment group reported on hair loss and

sexual activity. In patients' upset by hair loss, a clinically meaningful deterioration in this score was observed in both treatment groups from baseline to the end of taxane chemotherapy and persisted during targeted therapy. A decline in sexual enjoyment scores was considered clinically meaningful in both treatment groups at the end of taxane chemotherapy, and persisted during targeted therapy in the pertuzumab group only.

For the remaining symptom scores, which includes arm symptoms, breast symptoms, and future perspectives, no clinically meaningful differences in mean scores from baseline were observed between the treatment groups during the trial.

In the EMA report, it was reported that no major differences (≥ 5 percentage points) between the treatment groups were observed in the five EQ-5D domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[3]

Harms Outcomes

The safety analysis population was comprised of 4769 patients; 2364 in the pertuzumab-trastuzumab group and 2405 in the placebo-trastuzumab group. The safety analysis was performed according to the treatment received (at least one dose) by patients. In the pertuzumab group, the 2364 patients include the patients from the placebo group who erroneously received pertuzumab (n=24). In the placebo group, the 2405 patients includes patients from the pertuzumab group who only received chemotherapy (n=38). In both treatment groups, the safety analyses exclude the patients who did not receive assigned study drug.

AEs that occurred in the APHINITY trial are summarized in Table 10. The incidence of all-grade, treatment emergent AEs were 99.9% in the pertuzumab-trastuzumab group and 99.5% in the placebo-trastuzumab group.[3] The most common all-grade AEs (pertuzumab versus placebo) included diarrhea (71.2% versus 45.2%), nausea (69% versus 65.5%), alopecia (66.7% versus 66.9%), fatigue (48.8% versus 44.3%), vomiting (32.5% versus 30.5%), arthralgia (28.7% versus 32.5%), constipation (28.9% versus 31.6%), with the largest differences between treatment groups found for diarrhea and rash (25.8% versus 20.3%).[3] Incidence of most all-grade AEs were comparable between the treatment groups, and largely reflect toxicities associated with chemotherapy.[3]

The incidence of grade ≥3 AEs were higher in the pertuzumab group at 64.2%, compared to 57.3% in the placebo group. The higher incidence in the pertuzumab group was mainly driven by diarrhea (9.8% versus 3.7% with placebo). Overall, patients treated with pertuzumab had an earlier onset of diarrhea, which was worse in grade and longer in duration compared to placebo patients despite intervention with loperamide, which was administered in approximately double the amount of patients (35.6% versus 14.8%).[3] The frequency of grade ≥3 diarrhea was higher in patients treated with pertuzumab combined with non-anthracycline chemotherapy (18%) compared to anthracycline chemotherapy (7.5%).[28] After cessation of chemotherapy, the incidence of grade ≥3 diarrhea was 0.5% in the pertuzumab group and 0.2% in the placebo group. Other grade ≥3 AEs (pertuzumab versus placebo) included neutropenia (16.3% versus 15.7%), febrile neutropenia (12.1% versus 11.1%), anemia (6.9% versus 4.7%), and neutrophil count decreased (9.6% in both groups).

SAEs were slightly higher in the pertuzumab-trastuzumab treatment group compared to placebo (29.3% versus 24.3%), which were primarily attributable to

febrile neutropenia (8.8% versus 8.1%), diarrhea (2.5% versus 0.7%), and infections/infestations (6.8% versus 3.3%).[3]

Treatment delay/interruption and discontinuation due to AEs were slightly higher with pertuzumab-trastuzumab therapy compared to placebo-trastuzumab, for both any treatment (delay/interruption: 51.5% versus 44.2%; discontinuation: 13.1% versus 11.5%) and considering pertuzumab/placebo treatment (delay/interruption: 30.6% versus 26.3%; discontinuation: 7.0% versus 5.8%).[3] The most common AEs that lead to pertuzumab treatment discontinuations were ejection fraction declines, cardiac failure and diarrhea.[3]

The incidence of fatal AEs (deaths) were 0.8% in both the pertuzumab (n=18) and placebo (n=20) treatment groups.[3]

Cardiac Events

Primary cardiac events occurred in twice as many patients treated with the combination of pertuzumab-trastuzumab (0.7%, n=17) compared to placebo-trastuzumab (0.3%; n=8); Of these patients, 0.6% (n=15) and 0.2% (n=6) met the criteria for NYHA class III or IV heart failure with LVEF decline (primary cardiac endpoint of the trial), respectively, and two patients in each group (0.1%) died from cardiac causes. In the pertuzumab group, 15 of the 17 primary cardiac events occurred in patients treated with anthracycline chemotherapy. At the time of the data cut-off date, LVEF recovery was achieved in 53.3% (n=8/15) of patient in the pertuzumab group compared to 66.7% (n=4/6) in the placebo group; median time to LVEF recovery was longer in the pertuzumab-treated patients (27 weeks versus 16.3 weeks in placebo patients).[3]

Secondary cardiac events (asymptomatic or mildly symptomatic NYHA class II substantial LVEF decline) occurred in 2.7% (n=64) in the pertuzumab group and 2.8% (n=67) of patients in the placebo group; among these patients, LVEF recovery was achieved in 79.7% and 80.6% of patients, respectively, and median time-to acute recovery was comparable between treatment groups.[25]

Table 10: Summary of AEs in the safety analysis patient population of the APHINITY trial.

Event	Pertuzumab Group (N=2364)	Placebo Group (N=2405)
	no. of patients (%)	
Grade ≥3 adverse event	1518 (64.2)	1379 (57.3)
Neutropenia	385 (16.3)	377 (15.7)
Febrile neutropenia	287 (12.1)	266 (11.1)
Neutrophil count decreased	228 (9.6)	230 (9.6)
Diarrhea†	232 (9.8)	90 (3.7)
Anemia	163 (6.9)	113 (4.7)
Fatal adverse event‡	18 (0.8)	20 (0.8)
Primary cardiac event§	17 (0.7)	8 (0.3)
NYHA class III or IV heart failure and substantial decrease in LVEF¶	15 (0.6)	6 (0.2)
Definite or probable cardiac death	2 (0.1)	2 (0.1)
Secondary cardiac event‖	64 (2.7)	67 (2.8)
Identified automatically from LVEF assessments	50 (2.1)	47 (2.0)
Identified by cardiac advisory board	14 (0.6)	20 (0.8)

* The summary of grade 3 or higher adverse events includes adverse events with onset from the first dose of any study treatment through 28 days after the final dose of study treatment. The incidence of all other grade 3 or higher adverse events was lower than 5% in both safety analysis population groups. A summary of adverse events according to chemotherapy regimen is provided in Table S6 in the Supplementary Appendix. NYHA denotes New York Heart Association.

† For patients with diarrhea, early intervention with loperamide as well as fluid and electrolyte replacement was to be considered. The taxane dose had to be reduced by one dose level if grade 3 diarrhea occurred or unresolved grade 2 diarrhea required a delay of the next chemotherapy cycle.

‡ The fatal adverse events according to body system were neoplasms (benign, malignant, and unspecified) (9 patients in the pertuzumab group and 8 patients in the placebo group); cardiac disorders (2 and 3); infections and infestations (1 and 3); respiratory, thoracic, and mediastinal disorders (2 and 2); gastrointestinal disorders (0 and 3); injury, poisoning, and procedural complications (2 and 0); blood and lymphatic system disorders (1 and 0); metabolism and nutrition disorders (1 and 0); nervous system disorders (1 and 0); and psychiatric disorders (0 and 1). One patient in the pertuzumab group had a fatal adverse event that was reported in both the nervous system disorders and the injury, poisoning, and procedural complications body-system categories.

§ Primary cardiac events are counted over the whole trial period, including post-treatment follow-up. The 95% confidence interval (with Hauck–Anderson correction) for the between-group difference was 0.0 to 0.8 percentage points.

¶ A substantial decrease in left ventricular ejection fraction (LVEF) is defined as a decrease of 10 or more percentage points, to a value lower than 50%.

‖ Secondary cardiac events are counted up to the date of recurrence or the end of post-treatment follow-up, whichever occurs earlier, and are counted only for patients who have not had a primary cardiac event. The 95% confidence interval (with Hauck–Anderson correction) for the between-group difference was –1.0 to 0.9 percentage points.

From The New England Journal of Medicine. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. 2017; 377:122-131. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

6.4 Ongoing Trials

One ongoing RCT was identified that met the eligibility criteria of the pCODR systematic review. BOLD-1 (Table 11) is a phase 3, open-label trial assessing the efficacy of a shorter duration (9 weeks) of pertuzumab-trastuzumab combined with docetaxel chemotherapy compared to trastuzumab and docetaxel, with trastuzumab administered for a duration of one year.[30] The treatments can be given either before (neoadjuvant) or after (adjuvant) breast surgery. The trial hypothesis is that the shorter treatment regimen may be more efficacious than the comparator regimen despite is short duration.

Table 11: Ongoing trial of pertuzumab-trastuzumab combined with chemotherapy in HER-2 positive early breast cancer.

Trial	Inclusion Criteria	Intervention and Comparator	Trial Outcomes

BOLD-1
NCT02625441
 	
Design: Phase 3, open-label; randomization 1:1
 	
Estimated enrollment: n=1366
 	
Number of centres: Unknown
Number of countries: 1 (Finland)
 	
Study start date: December 2015
 	
Estimated primary analysis date: December 2022
 	
Estimated study completion date: June 2023
 	
Sponsor: Helsinki University Central Hospital
 	
Status: Recruiting
 	
Last updated: August 28, 2018
	<u>Key Inclusion Criteria:</u>
	• Women ≥ 18 years of age
	• Histologically confirmed invasive breast cancer
	• HER2 positive (assessed with in situ hybridization)
	• High-risk of recurrence with one of the following:
	  ○ pN0 with the longest invasive tumour diameter > 10 mm
	  ○ Histologically confirmed regional node positive disease
	
	<u>Key Exclusion Criteria:</u>
	• Distant metastases
	• Inflammatory breast cancer
	• Clinically significant (active) cardiac disease (CHF, symptomatic CAD and cardiac arrhythmia not well controlled with medication) or MI within the last year
	• Left ventricular ejection fraction less than 50% assessed by echocardiography or isotope cardiography
	• WHO PS >1
	• Pregnant or lactating
		<u>Intervention:</u>
		Short anti-HER2 treatment
		• Pertuzumab 840 mg iv, then 420 mg iv, 3-weekly for 3 cycles
		• Trastuzumab 8 mg/kg iv, then 6 mg/kg, 3-weekly for 3 cycles
		• Docetaxel 75 mg/m^2 iv, 3-weekly for 3 cycles
		
		<u>Comparator:</u>
		Standard anti-HER2 treatment
		• Trastuzumab 8 mg/kg iv, then 6 mg/kg, 3-weekly for 3 cycles
		• Docetaxel 75 mg/m2 iv, 3-weekly for 3 cycles, followed by,
		• Trastuzumab 6 mg/kg iv, 3-weekly for a total duration of one year
			<u>Primary:</u>
			• IDFS
			
			<u>Secondary:</u>
			• OS
			• Distant disease-free survival
			• Left ventricular ejection fractions
			• Safety

Abbreviations: CAD - coronary artery disease; **CHF** - congestive heart failure; **HER2**- human epidermal growth factor receptor 2; **IDFS** - invasive disease-free survival; **OS** - overall survival; **PS** - performance status; **WHO** - World Health Organization.			

SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review

COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

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 pertuzumab and trastuzumab for the adjuvant treatment of 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 thee 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: DETAILED METHODOLOGY AND LITERATURE SEARCH STRATEGY

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (March 2018) 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 pertuzumab/Perjeta, trastuzumab/Herceptin and breast cancer.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. 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 7, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - 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 San Antonio Breast Cancer Symposium (ABCS) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

Two members of the pCODR Methods Team were involved in the selection 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 independently 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.

LITERATURE SEARCH STRATEGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials March 2018, Embase 1974 to 2018 May 07, Ovid MEDLINE(R) ALL 1946 to 2018 May 07

#	Searches	Results
1	trastuzumab/ or (trastuzumab* or P188ANX8CK or Herceptin* or HSDB 8142 or HSDB8142 or MYL 1401O or MYL1401O or Ogivri* or Thiomab* or "PF 05280014" or PF05280014 or Rhumbab 4D5 or Rhumbab4D5 or 180288-69-1).ti,ab,kf,kw,hw,rn,nm.	46478
2	(pertuzumab* or 380610-27-5 or K16AIQ8CTM or HSDB 8141 or HSDB8141 or Omnitarg* or Perjeta* or 2C4 or R1273 or R 1273).ti,ab,kf,kw,hw,rn,nm.	4936
3	exp Breast Neoplasms/	743751
4	exp Breast/ or (breast* or mammar* or nipple*).ti,ab,kw,kf.	1093471
5	exp Neoplasms/ or (neoplasm* or neoplastic or malignan* or carcinoma* or cancer* or tumor* or tumour* or sarcoma*).ti,ab,kw,kf.	8973673
6	3 or (4 and 5)	977477
7	1 and 2 and 6	3452
8	7 use medall	549
9	7 use cctr	208
10	*trastuzumab/ or (trastuzumab* or Herceptin* or HSDB 8142 or HSDB8142 or MYL 1401O or MYL1401O or Ogivri* or Thiomab* or "PF 05280014" or PF05280014 or Rhumbab 4D5 or Rhumbab4D5).ti,ab,kw,dq.	28186
11	*pertuzumab/ or (pertuzumab* or HSDB 8141 or HSDB8141 or Omnitarg* or Perjeta* or 2C4 or R1273 or R 1273).ti,ab,kw,dq.	2743
12	exp Breast Cancer/	675407
13	exp Breast/ or (breast* or mammar* or nipple*).ti,ab,kw.	1093225
14	exp Neoplasm/ or (neoplasm* or neoplastic or malignan* or carcinoma* or cancer* or tumor* or tumour* or sarcoma*).ti,ab,kw.	8968917
15	12 or (13 and 14)	962950
16	10 and 11 and 15	1905
17	16 use oemezd	1224
18	17 and conference abstract.pt.	605
19	17 not 18	619
20	8 or 9 or 19	1376
21	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.	1083125
22	(Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.	845401
23	Multicenter Study.pt.	309964
24	Clinical Studies as Topic/	154126
25	exp Clinical Trial/ or exp Clinical Trials as Topic/ or exp "Clinical Trial (topic)"/	2648054

26	Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/	459392
27	Randomization/	172120
28	Random Allocation/	189502
29	Double-Blind Method/	398016
30	Double Blind Procedure/	149593
31	Double-Blind Studies/	256645
32	Single-Blind Method/	72669
33	Single Blind Procedure/	31289
34	Single-Blind Studies/	74066
35	Placebos/	325553
36	Placebo/	324828
37	Control Groups/	112593
38	Control Group/	112497
39	Cross-Over Studies/ or Crossover Procedure/	131272
40	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3776404
41	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	739602
42	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2611
43	(control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf,kw.	8540527
44	(clinical adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	5956383
45	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	91270
46	(phase adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	440420
47	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	174384
48	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	653246
49	allocated.ti,ab,hw.	165395
50	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	103803
51	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	21554
52	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	822
53	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	9695
54	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	15756
55	trial.ti,kf,kw.	809970
56	or/21-55	13413950
57	exp animals/	46353803
58	exp animal experimentation/	2225929
59	exp models animal/	1647880
60	exp animal experiment/	2225929
61	nonhuman/	5436840
62	exp vertebrate/	45016884
63	animal.po.	0

64	or/57-63	48037553
65	exp humans/	37200188
66	exp human experiment/	406132
67	human.po.	0
68	or/65-67	37201743
69	64 not 68	10836831
70	56 not 69	10798666
71	18 and 70	452
72	remove duplicates from 71	437
73	limit 72 to english language	437
74	limit 73 to yr="2013 -Current"	366
75	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1082349
76	Randomized Controlled Trial/	961922
77	exp Randomized Controlled Trials as Topic/	270470
78	"Randomized Controlled Trial (topic)"/	144998
79	Controlled Clinical Trial/	553864
80	exp Controlled Clinical Trials as Topic/	281416
81	"Controlled Clinical Trial (topic)"/	9434
82	Randomization/	172120
83	Random Allocation/	189502
84	Double-Blind Method/	398016
85	Double Blind Procedure/	149593
86	Double-Blind Studies/	256645
87	Single-Blind Method/	72669
88	Single Blind Procedure/	31289
89	Single-Blind Studies/	74066
90	Placebos/	325553
91	Placebo/	324828
92	Control Groups/	112593
93	Control Group/	112497
94	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3776404
95	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	739602
96	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2611
97	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2455152
98	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	91270
99	allocated.ti,ab,hw.	165395
100	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	103803
101	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	21554

102 (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	822
103 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	9695
104 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	15756
105 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	118635
106 or/75-105	5442481
107 20 and 106	583
108 remove duplicates from 107	423
109 limit 108 to english language	412
110 74 or 109	778

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found	Time
#16	**Search (#13 AND #14) Filters: English**	24	14:27:39
#15	**Search (#13 AND #14)**	24	14:27:30
#14	**Search ((publisher[sb] OR 2018/04/24:2018/05/08[edat]))**	539888	14:27:13
#13	**Search (#9 AND #12)**	540	14:26:45
#12	**Search (#10 OR #11)**	383038	14:26:36
#11	**Search "Breast Neoplasms"[Mesh]**	262647	14:26:29
#10	**Search ((("Breast"[Mesh] OR breast*[tiab] OR mammar*[tiab] OR nipple*[tiab]) AND ("Neoplasms"[Mesh] OR neoplasm*[tiab] OR neoplastic[tiab] OR malignan*[tiab] OR carcinoma*[tiab] OR cancer*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR sarcoma*[tiab]))**	349730	14:26:23
#9	**Search (#7 AND #8)**	619	14:25:32
#8	**Search (("pertuzumab" [Supplementary Concept] OR (pertuzumab*[tiab] OR K16AIQ8CTM[tiab] OR HSDB 8141[tiab] OR HSDB8141[tiab] OR Omnitarg*[tiab] OR Perjeta*[tiab] OR ((monoclonal[tiab] OR rhumab[tiab]) AND 2C4[tiab]) or R1273 or R 1273)))**	1105	14:25:21
#7	**Search (("Trastuzumab"[Mesh] OR (trastuzumab*[tiab] OR P188ANX8CK[tiab] OR Herceptin*[tiab] OR HSDB 8142[tiab] OR HSDB8142[tiab] OR MYL 1401O[tiab] OR MYL1401O[tiab] OR Ogivri*[tiab] OR Thiomab*[tiab] OR PF 05280014[tiab] OR PF05280014[tiab] OR Rhumbab 4D5[tiab] OR Rhumbab4D5[tiab]))**	9986	14:25:03

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

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

Search: trastuzumab, pertuzumab, Herceptin, Perjeta

Select international agencies including:

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

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: trastuzumab, pertuzumab, Herceptin, Perjeta

Conference abstracts:

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

Search: trastuzumab, pertuzumab, Herceptin, Perjeta - 2018

San Antonio Breast Cancer Symposium
https://www.sabcs.org/

Search: trastuzumab, pertuzumab, Herceptin, Perjeta - 2017

REFERENCES

1. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer.[Erratum appears in N Engl J Med. 2017 Aug 17;377(7):702; PMID: 28700263]. *N Engl J Med.* 2017;377(2):122-131.
2. Hoffman-La Roche response to pCODR checkpoint meeting questions [additional manufacturer's information]. Mississauga (ON): Hoffman-La Roche Limited; 2018 Jun 15.
3. Committee for Medicinal Products for Human Use (CHMP). CHMP extension of indication variation assessment report: Perjeta. *(Procedure No. EMEA/H/C/002547/II/0034)*. London (GB): European Medicines Agency; 2018: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002547/WC500251174.pdf. Accessed 2018 Sep 10.
4. Hoffman-La Roche responses to request for additional information [additional manufacturer's information]. Mississauga (ON): Hoffman-La Roche Limited; 2018 Aug 28.
5. Baselga J, Petersen JA, Clark E, Barton C, Restuccia E, Procter M, et al. Patient (pt)-reported function and symptoms in APHINITY: A randomized comparison of chemotherapy (C) + trastuzumab (H) + placebo (Pla) versus C + H + pertuzumab (P) as adjuvant therapy in pts with HER2-positive early breast cancer (EBC). *2018 ASCO Annual Meeting*2018: https://meetinglibrary.asco.org/record/162838/poster. Accessed 2018 Sep 10.
6. Hoffman-La Roche response to pCODR checkpoint meeting follow-up questions [additional manufacturer's information]. Mississauga (ON): Hoffman-La Roche Limited; 2018 Jun 28.
7. Sedgwick P. The importance of statistical power. *BMJ.* 2013;347:f6282.
8. Swain SM, Ewer MS, Viale G, Delaloge S, Ferrero JM, Verrill M, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): A phase II, open-label, multicenter, multinational cardiac safety study. *Ann Oncol.* 2018;29(3):646-653.
9. pCODR Expert Review Committee (pERC) final recommendation: Perjeta or Perjeta-Herceptin combopack (pertuzumab). Ottawa (ON): CADTH; 2015: https://www.cadth.ca/sites/default/files/pcodr/pcodr_pertuzumab_perjeta_nbc_fn_rec.pdf. Accessed 2018 Sep 10.
10. Gianni L, Bisagni G, Colleoni M, Del Mastro L, Zamagni C, Mansutti M, et al. Neo-adjuvant treatment with trastuzumab and pertuzumab associated with palbociclib and fulvestrant in HER2-positive and ER-positive breast cancer: effect on Ki67 during and after treatment. A phase II Michelangelo study. *Cancer research Conference: 39th annual CTRC AACR san antonio breast cancer symposium United states.* 2017;77(4 Supplement 1).
11. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384(9938):164-172.
12. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2017. Toronto (ON): Canadian Cancer Society; 2017: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2017-EN.pdf. Accessed 2018 Sep 10.
13. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med.* 2005;353(16):1659-1672.
14. Baselga J, Cortes J, Kim SB, Im SA, Hegg R, Im YH, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med.* 2012;366(2):109-119.

15. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-734.
16. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(1):25-32.
17. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016;17(6):791-800.
18. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). *Journal of Clinical Oncology Conference*. 2015;33(15 SUPPL. 1).
19. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol*. 2013;24(9):2278-2284.
20. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast bancer. *N Engl J Med*. 2017;377(2):122-131.
21. Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol*. 2007;25(15):2127-2132.
22. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783-792.
23. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1673-1684.
24. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365(14):1273-1283.
25. [Pr]Perjeta[R] (pertuzumab): 420 mg/14 mL vial for intravenous infusion [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2018 Aug 30: http://www.rochecanada.com/content/dam/roche_canada/en_CA/documents/Research/ClinicalTrialsForms/Products/ConsumerInformation/MonographsandPublicAdvisories/Perjeta/Perjeta_PM_E.pdf. Accessed 2018 Sep 10.
26. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997-4013.
27. Breast cancer: Economic impact and labour force re-entry 2010. Ottawa (ON): Canadian Breast Cancer Network; 2018: https://www.cancerandwork.ca/breast-cancer-economic-impact-and-labour-force-re-entry-2010/. Accessed 2018 Sep 10.
28. Bines J, De Azambuja E, Zardavas D, Procter M, Restuccia E, Viale G, et al. Incidence and management of diarrhea with adjuvant pertuzumab and trastuzumab in HER2-Positive breast cancer. *Cancer Research Conference: San Antonio Breast Cancer Symposium, SABCS*. 2017;78(4 Supplement 1).
29. Hoffmann-La Roche. A study of pertuzumab in addition to chemotherapy and trastuzumab as adjuvant therapy in participants with human epidermal growth receptor 2 (HER2)-positive primary breast cancer (APHINITY). *ClinicalTrials.gov*. Bethesda (MD): U. S.

National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/study/NCT01358877?term=NCT01358877&rank=1&sect=Xv56. Accessed 2018 Sep 10.
30. Helsinki University Central Hospital. Adjuvant trastuzumab, pertuzumab plus docetaxel in the treatment of early HER2-positive breast cancer (BOLD-1). *ClinicalTrial.gov*. Bethesda (MD): U. S. National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/NCT02625441?term=NCT02625441&rank=1. Accessed 2018 Sep 10.