pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Pertuzumab and trastuzumab (Perjeta-Herceptin Combo Pack)

Submitted Reimbursement Request:
In combination with trastuzumab and chemotherapy for 18 cycles for the treatment of human epidermal growth factor receptor 2 (HER2) -positive early breast cancer patients at high risk of recurrence. High risk of recurrence is defined as either node-positive or hormone receptor-negative disease.

Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: August 30, 2018	**Submission Date:** April 9, 2018
Initial Recommendation: October 4, 2018	**Final Recommendation:** November 29, 2018

Approximate Per-Patient Drug Costs	Pertuzumab costs $7.93 per mg • At the recommended dose of 840 mg (loading dose) administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg (maintenance dose) administered over a period of 30 to 60 minutes pertuzumab costs: • $6,657.10 (loading dose) • $3,328.55 (maintenance dose)

pERC RECOMMENDATION

pERC does not recommend reimbursement of pertuzumab in combination with trastuzumab and chemotherapy for the treatment of human epidermal growth factor receptor 2 (HER2) -positive early breast cancer patients at high risk of recurrence. High risk of recurrence is defined as either node-positive or hormone receptor-negative disease.

The Committee made this recommendation because it was not satisfied that there is a clinically meaningful net benefit of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive early breast cancer at high risk of recurrence. The Committee noted that there was a high level of uncertainty around the magnitude of the invasive disease-free survival (IDFS) benefit given that the trial was not designed to detect treatment effects within subgroups and that there was no proven difference in overall survival (OS). pERC was uncertain about whether pertuzumab adequately addresses the need for more effective therapies in patients at high risk of recurrence.

Although pERC acknowledged that patients value additional treatment options, the Committee was not satisfied that the addition of pertuzumab to adjuvant treatment with trastuzumab and chemotherapy addresses the key outcomes that patients have indicated they value, such as reduced

	side effects and the prevention of disease recurrence. pERC could not draw a conclusion on the cost-effectiveness of pertuzumab in combination with trastuzumab and chemotherapy in the adjuvant setting due to the uncertainty surrounding the incremental benefits used in the economic model.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC noted that future trials of adjuvant breast cancer therapy comparing pertuzumab in combination with trastuzumab and chemotherapy with currently available treatments in Canada should consider either overall survival (OS) as the primary end point or a validated surrogate end point for OS in this disease setting. Further, trials should be designed to detect a difference in treatment effect in the population requested for reimbursement. In addition, pERC acknowledged that APHINITY is currently ongoing. The estimated final OS analysis with mature OS data is estimated to occur 9 to 10 years after the last patient randomized (i.e., 2023). pERC noted that these OS results could, by themselves, form the basis of a resubmission to pCODR.

SUMMARY OF pERC DELIBERATIONS

Breast cancer remains one of the most common malignancies affecting Canadian patients, with 26,300 new cases diagnosed in 2017. The majority of these cases represent early stage, potentially curable disease. A proportion of these breast cancer tumours (15% to 30%) are human epidermal growth factor receptor 2 (HER2) -positive, which has been associated with poorer prognosis and more aggressive disease. Up to one in four HER2-positive patients with early breast cancer experience recurrence or death within 10 years of diagnosis. The current standard of care for the adjuvant treatment of patients with HER2-positive early breast cancer is trastuzumab plus chemotherapy, based on evidence of an OS benefit. pERC agreed that there is a need for more effective and less toxic therapies that prevent disease recurrence and improve OS.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of one randomized, placebo-controlled, phase III trial (APHINITY), that evaluated the efficacy and safety of pertuzumab in combination with trastuzumab (Perjeta-Herceptin Combo Pack) and chemotherapy compared with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer. The Committee noted that the reimbursement request was specifically for two patient subgroups within the APHINITY trial: patients with (1) node-positive or (2) hormone receptor-negative disease. pERC noted that the pre-specified subgroup analyses for the primary outcome, IDFS, demonstrated a modest statistically significant improvement in favour of pertuzumab and trastuzumab in the node-positive subgroup, but not in the hormone receptor-negative subgroup. The Committee discussed that there was a high level of uncertainty around the magnitude of the IDFS benefit given that the subgroup analyses were pre-specified but exploratory and therefore not designed to detect treatment effects within subgroups. Furthermore, no adjustments were made for multiple testing, which increases the risk of a false-positive result, and the statistical tests of interaction were non-significant, suggesting that neither node-positive nor hormone receptor-negative status was associated with a statistically significant difference in treatment effect. Therefore, pERC agreed with the pCODR Methods Team that it was not possible to draw firm conclusions on the IDFS results from the two subgroups of interest.

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.

In addition, pERC noted that the results for OS (a secondary outcome) are immature at present and that the impact of the pertuzumab combination on OS is unknown. pERC acknowledged that patients with early breast cancer may relapse after many years and have a relatively long survival, making it unlikely to detect any difference in OS with only a short follow-up period. Furthermore, the Committee considered that there is uncertainty about whether IDFS is a reliable surrogate outcome for OS in the breast cancer context. pERC noted that IDFS is a modified, non-standard composite end point that has not been validated in the published literature. In addition, pERC identified that a closely related outcome, disease-free survival (DFS), has also not been found to be a reliable predictor for OS in trials of breast cancer conducted in the adjuvant setting. Given the lack of a significant difference in OS, pERC agreed with the registered clinicians that there was high uncertainty around whether the modest IDFS benefit observed with pertuzumab and trastuzumab was clinically meaningful.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter suggesting that a proven difference in OS at the time of primary IDFS analysis is an unreasonable expectation. pERC discussed the response provided by the pCODR Clinical Guidance Panel

(CGP) in the pCODR Final Clinical Guidance Report that, given patients with early breast cancer may relapse after many years, it seemed reasonable to confirm the results with more mature OS data at the pre-specified protocol time. However, pERC reiterated that in the absence of mature OS data, there is high uncertainty around whether the modest IDFS benefit observed with pertuzumab and trastuzumab was clinically meaningful, given that it is unclear whether IDFS is a reliable surrogate outcome for OS in this context.

pERC deliberated on the toxicity profile of pertuzumab in combination with trastuzumab and chemotherapy and noted that the incidence of all-grade treatment-related adverse events (AEs) was broadly similar between study groups, more apparent during the chemotherapy portion of treatment, and consistent with the safety profile of this combination in the metastatic setting. The most common all-grade AEs included diarrhea, nausea, alopecia, fatigue, vomiting, arthralgia, and constipation. pERC highlighted that diarrhea was worse in severity and longer in duration compared with placebo patients and was among the main AEs leading to treatment discontinuation or dose modification; furthermore, this was in line with results for the pertuzumab combination in the metastatic setting. pERC noted that primary cardiac events occurred in twice as many patients treated with the pertuzumab combination compared with placebo. However, pERC noted that the absolute numbers remained low and that the majority of primary cardiac events occurred in patients treated with anthracycline chemotherapy, which by itself is associated with cardiac events. Overall, pERC agreed with the CGP that pertuzumab in combination with trastuzumab and chemotherapy has a manageable safety profile.

Overall quality of life (QoL) was similar between the two study arms and remained stable during treatment. While QoL showed a clinically meaningful decrease during chemotherapy, scores generally returned to baseline during targeted treatment. pERC noted, however, that diarrhea symptoms, which worsened in both groups mainly during chemotherapy treatment, continued to show a clinically meaningful increase during the entire treatment period for the pertuzumab-trastuzumab group. The Committee concluded that, overall, there appeared to be no detriment to QoL from the treatment with the pertuzumab combination compared to the control arm.

pERC is not satisfied that there is a clinically meaningful net benefit to pertuzumab, trastuzumab, and chemotherapy compared with trastuzumab and chemotherapy in the adjuvant treatment of HER2-positive early breast cancer in patients with node-positive or hormone receptor–negative disease. In making this conclusion, pERC considered the high level of uncertainty around the magnitude of the IDFS benefit given the trial was not designed to detect treatment effects within subgroups and that there was no proven difference in OS. pERC considered that neither IDFS nor DFS are as yet validated surrogate outcomes for OS in trials of breast cancer conducted in the adjuvant setting. While pERC acknowledged that pertuzumab in combination with trastuzumab and chemotherapy had a manageable toxicity profile and showed no significant detriment in QoL, it was uncertain whether pertuzumab adequately addresses the need for more effective therapies in patients with HER2-positive early breast cancer who have node-positive or hormone receptor–negative disease.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter suggesting that there is a clinically meaningful net clinical benefit of pertuzumab in combination with trastuzumab and chemotherapy because the APHINITY trial met its primary outcome of IDFS in the intention-to-treat population; therefore, it would be appropriate to investigate the consistency of the primary analysis results across pre-specified subgroups. In addition, the submitter noted that pERC's assessment of clinical benefit is incongruent with the opinions of the CGP, which stated there is likely a clinically meaningful net overall clinical benefit among lymph node-positive HER2-positive early breast cancer patients based on pre-specified subgroup analyses. pERC discussed clarifications provided by the pCODR Methods Lead in the pCODR Final Clinical Guidance Report that, as a protocol amendment increased the sample size of APHINITY by about 1,000 patients, it is possible APHINITY was overpowered. The trial detected an absolute difference in IDFS between treatment groups that was smaller (0.9%) than the difference (2.6%) that was pre-specified as being clinically significant. pERC agreed that it is unclear if the observed small absolute difference in IDFS between the treatment groups is clinically significant. Furthermore, pERC agreed with the pCODR Methods Lead that as the APHINITY trial's ITT analysis for the primary outcome was statistically significant, it was appropriate to investigate the consistency of the results in pre-specified subgroups. However, pERC reiterated that the subgroup analyses in APHINITY were not designed to make statistical inferences as they were exploratory in nature, not designed to test for differences, not controlled for multiple testing, and tests for statistical interaction were non-significant. Therefore, pERC reiterated that the subgroup analyses do not clearly

demonstrate that the combination of pertuzumab-trastuzumab is more efficacious in lymph node-positive patients or hormone receptor-negative patients. Notwithstanding the opinion of the CGP, the Committee, therefore, upheld its initial conclusion that it was not satisfied that there is a clinically meaningful net benefit to pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy in the adjuvant treatment of HER2-positive early breast cancer in patients with node-positive or hormone receptor–negative disease.

Also upon reconsideration, pERC discussed feedback from the submitter that the US FDA, the European Medicines Agency, and Health Canada have approved the use of pertuzumab in the adjuvant setting. The submitter noted that this position is further supported by recommendations in the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) guidelines. pERC noted that regulatory agencies as well as clinical practice guidelines have a different purpose than health technology assessment bodies. The former needs to determine a minimum efficacy level and acceptable safety profile, while the purpose of the latter is to optimize patient care, informed by safety and efficacy of alternative care options. Health technology assessment is broader in that it examines the comparative effectiveness of different treatment strategies looking at multiple dimensions while aiming to provide a balance between the values, needs, preferences, and perspectives of patients and those of society.

pERC considered that patients said they value having access to effective treatment options that reduce the risk of recurrence, maintain QoL, maintain mobility and productivity, have minimal side effects, require minimal medical appointments, and afford the ability to continue child care duties. pERC acknowledged that compared with adjuvant trastuzumab and chemotherapy, the pertuzumab combination offers an additional treatment option with a similar impact on QoL. However, the Committee was not satisfied that the addition of pertuzumab to adjuvant treatment addresses key outcomes that patients value, such as reduced side effects and the prevention of disease recurrence.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter suggesting that pertuzumab in combination with trastuzumab is aligned with patient values because it provides an additional almost 25% reduction in the risk of recurrence or death, has a tolerable safety profile, and is not associated with a significant detriment to QoL. In response to the submitter's feedback, pERC reiterated that there was a high level of uncertainty around the magnitude of the IDFS benefit in the node-positive and hormone receptor-negative patient subgroups due to the trial not being designed to detect treatment effects within subgroups. In addition, the Committee noted that while pertuzumab in combination with trastuzumab and chemotherapy has a manageable safety profile, it is not less toxic than trastuzumab and chemotherapy. Therefore, pERC reiterated that it was not satisfied that the addition of pertuzumab to adjuvant treatment addresses key outcomes that patients value, such as reduced side effects and the prevention of disease recurrence.

pERC deliberated on the cost-effectiveness of pertuzumab, trastuzumab, and chemotherapy compared with trastuzumab and chemotherapy for the adjuvant treatment of HER2-positive early breast cancer in patients who have node-positive or hormone receptor–negative disease. pERC agreed that the estimates of incremental effect are largely based on a key clinical assumption that differences in the rate of IDFS can lead to improvement in OS, especially given the small magnitude of IDFS improvement observed in the trial so far. Given the Committee's lack of confidence in the clinical effect estimates for IDFS derived from the subgroup analyses and the uncertainty whether IDFS is a reliable surrogate outcome for OS, pERC was unsure that there is a clinically meaningful net clinical benefit. Therefore, pERC could not draw a conclusion on the cost-effectiveness and could not determine the incremental cost-effectiveness ratio (ICER) of pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy for the adjuvant treatment of HER2-positive early breast cancer in patients who have node-positive or hormone receptor–negative disease.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter suggesting that it is possible to estimate an ICER. pERC discussed clarifications provided by the pCODR Economic Guidance Panel (EGP) in the pCODR Final Economic Guidance Report stating that the EGP agreed with pERC that the subgroup analyses were pre-specified but exploratory and, therefore, the trial was not designed to detect treatment effect differences based on subgroups. The EGP noted that there was a lack of evidence regarding a difference in treatment effect in each subgroup, which may impact the interpretation of the magnitude of incremental effectiveness, and the resulting ICER. In addition, the EGP stated that, if IDFS is not accepted as a meaningful surrogate for OS in this patient population by pERC, the results of the economic model are difficult to interpret as the model is

dependent on the acceptance of this outcome. pERC agreed to uphold its initial position that it could not draw a conclusion on the cost-effectiveness and could not determine the incremental cost-effectiveness ratio (ICER) of pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy for the adjuvant treatment of HER2-positive early breast cancer in patients who have node-positive or hormone receptor–negative disease.

pERC considered the feasibility of implementing a reimbursement recommendation for the pertuzumab combination for the adjuvant treatment of HER2-positive early breast cancer in patients who have node-positive or hormone receptor–negative disease. The Committee agreed with the pCODR Provincial Advisory Group that, for this submission, pertuzumab is available only in a package that includes both pertuzumab and trastuzumab (Perjeta-Herceptin Combo Pack) and is a barrier to implementation. Although pertuzumab is administered at a fixed dose, trastuzumab is administered based on weight. While it is possible that excess trastuzumab can be used for other patients, the burden on inventory management resources would be substantial. pERC acknowledged feedback from the submitter that pertuzumab is available in Canada as a single vial. Making pertuzumab available on its own for the present indication, instead of being available only in a combination kit, would be preferred for implementation. In addition, pERC noted that pertuzumab is a high-cost drug and that the submitted Ontario-specific budget impact was substantial and likely underestimated. pERC acknowledged that, according to the EGP's reanalysis, the submitted incremental three-year budget impact (1) increased by about 14% if the market share was increased to 50%, 64%, and 75% in years 1, 2, and 3, and (2) increased by about 12.5% if the proportion of patients assumed to receive adjuvant treatment was increased by 10% from baseline. Therefore, pERC concluded that the estimated substantial budget impact was a barrier to implementation.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from two patient advocacy groups: The Canadian Breast Cancer Network
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, The Canadian Breast Cancer Network
- Registered clinicians
- PAG
- Submitter, Hoffmann-La Roche Limited.

The pERC Initial Recommendation was to not recommend reimbursement of pertuzumab in combination with trastuzumab and chemotherapy for the treatment of human epidermal growth factor receptor 2 (HER2) -positive early breast cancer patients at high risk of recurrence. High risk of recurrence is defined as either node-positive or hormone receptor–negative disease.

Feedback on the pERC Initial Recommendation indicated that PAG agreed with the Initial Recommendation. The registered clinicians agreed in part with the Initial Recommendation. Both the patient advocacy group and the submitter disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the efficacy and safety of pertuzumab in combination with trastuzumab (Perjeta-Herceptin Combo Pack) and chemotherapy compared with trastuzumab and chemotherapy for the adjuvant treatment of patients with human epidermal growth factor receptor 2 (HER2) -positive early breast cancer.

Studies included: One randomized, placebo-controlled, phase III trial

The pCODR systematic review included one randomized, placebo-controlled, phase III trial: APHINITY. The APHINITY trial evaluated the efficacy and safety of pertuzumab in combination with trastuzumab (Perjeta-Herceptin Combo Pack) and chemotherapy compared with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer.

A total of 4,805 patients were randomized (1:1) in APHINITY, with 2,400 assigned to pertuzumab, trastuzumab, and chemotherapy and 2,404 to placebo, trastuzumab and chemotherapy. 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 kilogram of body weight as a loading dose, followed by 6 mg/kg every three weeks) beginning with the first cycle of chemotherapy and continuing for a maximum of 18 treatment cycles (one year). Patients received anti-HER2 treatment in combination with chemotherapy according to one of the following dosing schedules: three or four cycles (every three weeks) of 5-fluorouracil plus either epirubicin or doxorubicin plus cyclophosphamide, followed by three or four cycles (every three weeks) of docetaxel or 12 weekly cycles of paclitaxel; four cycles (every three weeks or every two weeks) of cyclophosphamide plus either doxorubicin or epirubicin, followed by either four cycles (every three weeks) of docetaxel or 12 weekly cycles of paclitaxel; or six cycles (every three weeks) of docetaxel plus carboplatin. Pertuzumab was planned to be administered in combination with trastuzumab 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-based or taxane-based chemotherapy. Pertuzumab and trastuzumab should start on day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued. In patients receiving an anthracycline-based regimen, pertuzumab and trastuzumab should

be administered following completion of the anthracycline treatment. Dose delays and interruptions were permitted in the trial to assess or manage toxicities associated with treatment; however, patients were withdrawn from the study if dose delays of targeted drugs exceeded more than two treatment cycles. Dose modifications were not permitted for either targeted drug but were allowed for chemotherapy according to specified guidelines in the trial protocol.

The median durations of study treatment (targeted therapy and chemotherapy) and targeted therapy were the same in both groups at 64 weeks and 55 weeks, respectively. 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.

Patient populations: Median age 51 years; majority of patients with hormone receptor-positive (64%) and node-positive disease (63%)

Overall, the baseline characteristics of patients were well balanced between the two treatment groups. 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 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The majority of patients had hormone receptor-positive (64%) and node-positive disease (63%). When the entire trial population is considered, approximately 6% of patients had tumours < 1 cm in size. The trial enrolled 11 (< 1%) male patients.

The primary analysis population is comprised of 4,804 patients, and not the 4,805 patients originally randomized; one patient in the placebo-trastuzumab group was excluded after randomization on the basis of falsification of personal information.

Most patients in the trial were randomized into the trial under protocol version A (76%). 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 3,806 to 4,800 patients) that included only node-positive patients, and the addition of protocol version as a stratification factor. According to the pCODR Methods Team, it is possible that, as a result of protocol amendment B, the trial might have been overpowered, thereby increasing the risk of type I error (finding an association which is statistically significant but not clinically meaningful).

Key efficacy results: Modest difference in IDFS in favour of pertuzumab; trial not designed to detect differences within subgroups

The primary outcome of the APHINITY trial was invasive disease–free survival (IDFS), a composite end point, 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 (standardized definitions for efficacy end points [STEEP] definition, which includes second primary invasive non-breast cancers), disease-free survival (DFS) (includes second primary invasive non-breast cancers and non-invasive breast cancer), OS, relapse-free interval, and distant relapse-free interval. Patient-reported health-related quality of life (QoL) was considered an exploratory outcome of the trial.

The trial met its primary outcome demonstrating a statistically significant improvement in IDFS in the pertuzumab treatment group (hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.66 to 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 events to occur in both treatment groups: 4.7% (n = 112) in the pertuzumab group and 5.8% (n = 139) in the placebo group.

Exploratory 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 to 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 to 0.91), had node-positive disease (HR 0.77; 95% CI, 0.62 to 0.96), and tumour size less than 2 cm (HR 0.62; 95% CI, 0.42 to 0.92); however, tests for interaction for these subgroups (and all other subgroup analyses but one) were non-significant, suggesting that the treatment effect was not significantly different among the categories of patients in each subgroup examined.

The secondary outcomes of the trial were tested sequentially in the following order: IDFS (STEEP definition), DFS, and OS. 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 to 1.21; *P* = 0.47). The OS data are currently immature with an information fraction of 26%.

Patient-reported outcomes: Overall no difference between treatment arms

QoL outcomes (an exploratory end point of the APHINITY trial), were collected using the EORTC (European Organization for Research and Treatment of Cancer) Quality of Life Questionnaire–Core 30 (QLQ-C30), EORTC QLQ breast-specific module (BR23), and EQ-5D (EuroQol 5-Dimensions) questionnaires. QoL data were collected before disease recurrence.

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.

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 targeted treatment, and the deterioration was clinically meaningful in the pertuzumab group but not in the placebo group.

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. Among approximately 300 patients who reported on hair loss and sexual activity, 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, and 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).

Safety: Manageable toxicity profile, similar between groups

The incidence of all-grade treatment-related adverse events (AEs) was broadly similar between study groups. 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%), with the largest differences between treatment groups found for diarrhea and rash (25.8% versus 20.3%). The incidence of grade ≥ 3 AEs was higher in the pertuzumab group at 64.2% than in the placebo group at 57.3%. 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 with 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 decreased neutrophil count (9.6% in both groups).

Serious AEs were slightly higher in the pertuzumab-trastuzumab treatment group compared with the placebo group (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%).

Primary cardiac events occurred in twice as many patients treated with the combination of pertuzumab-trastuzumab (0.7%, n = 17) than with placebo-trastuzumab (0.3%; n = 8); Of these patients, 0.6% (n = 15) and 0.2% (n = 6) met the criteria for NYHA (New York Heart Association) class III or IV heart failure with

left ventricular ejection fraction (LVEF) decline, respectively, and two patients in each group (0.1%) died from cardiac causes. Primary cardiac events occurred in 22 of 3,728 patients who received anthracycline chemotherapy. Of those, 15 (0.8%) patients in the pertuzumab group experienced a cardiac event, whereas 7 (0.4%) patients in the control group experienced a cardiac event. Primary cardiac events occurred in 3 of 1,038 patients who received non-anthracycline chemotherapy. Of those, 2 (0.4%) patients in the pertuzumab group experienced a cardiac event, whereas 1 (0.2%) patients in the control group experienced a cardiac event. In the pertuzumab group, 15 of the 17 primary cardiac events occurred in patients treated with anthracycline chemotherapy.
Treatment delay/interruption and discontinuation of one or more study drugs (including chemotherapy) due to AEs were slightly higher with pertuzumab-trastuzumab therapy compared with 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 with placebo-trastuzumab (delay/interruption, 30.6% versus 26.3%; discontinuation, 7.0% versus 5.8%). The most common AEs that led to pertuzumab treatment discontinuations were ejection fraction declines, cardiac failure, and diarrhea.
The incidence of fatal AEs (deaths) was 0.8% in both the pertuzumab (n = 18) and placebo (n = 20) treatment groups.

Need and burden of illness: Need for effective treatments that reduce side effects, prevent disease recurrence, and improve overall survival

Breast cancer remains one of the most common malignancies affecting Canadian patients, with 26,300 new cases diagnosed in 2017. The majority of these cases represent early stage, potentially curable disease. A proportion of these breast cancer tumours (15% to 30%) are HER2-positive, which has been associated with poorer prognosis and more aggressive disease. Up to one in four HER2-positive patients with early breast cancer experience recurrence or death within 10 years of diagnosis. The current standard of care for the adjuvant treatment of patients with HER2-positive early breast cancer is trastuzumab plus chemotherapy, based on evidence of a survival benefit. According to the pCODR Clinical Guidance Panel (CGP) 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. There is a need for more effective and less toxic therapies that prevent disease recurrence and improve overall survival (OS).

Registered clinician input: APHINITY demonstrated minimal improvement; uncertain if clinically meaningful given the lack of a proven difference in OS, alternative treatments available

Two clinician inputs (one joint and one individual input) were provided for this submission. In terms of the clinical benefit, the registered clinicians providing the joint input noted 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 IDFS in the APHINITY trial, they were unsure if the observed benefit was clinically meaningful given the lack of a significant difference in OS. In addition, the clinicians did not believe this treatment fills an unmet need because there are effective treatments available already and the trial demonstrated only 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.

PATIENT-BASED VALUES

Values of patients with HER2-positive early breast cancer: Effectiveness, prevention of disease recurrence, maintenance of quality of life, reduction in side effects

One patient advocacy group provided input for this submission for the treatment of HER2-positive early breast cancer. Patients reported that key 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. In addition, according to patients, 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, patients can incur substantial costs associated with treatment and disease management.

In terms of expectations for alternative treatment options, patients value having access to effective therapies that reduce the risk of recurrence, maintain QoL, maintain mobility and productivity, have minimal side effects, require minimal medical appointments, and afford the ability to continue child care duties.

Patient values on treatment: Tolerable quality of life, manageable side effects

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 canker sores, but ranked her QoL 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 QoL 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 toward the combination treatment, reporting gratitude at having access to this treatment and expressing that more women should have access to this treatment.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the patient advocacy group suggesting that pertuzumab in combination with trastuzumab and chemotherapy addresses key outcomes that patients value because it provides another treatment option with improvements in IDFS while still maintaining a good QoL. Furthermore, the patient advocacy group suggested that pertuzumab in combination with trastuzumab and chemotherapy could benefit higher risk populations including node-positive patients. In response to the patient advocacy group's feedback, pERC reiterated that there was a high level of uncertainty around the magnitude of the IDFS benefit in node-positive and hormone receptor-negative patient subgroups due to the trial not being designed to detect treatment effects within subgroups. In addition, the Committee noted that while pertuzumab in combination with trastuzumab and chemotherapy has a manageable safety profile, it is not less toxic than trastuzumab and chemotherapy. Furthermore, pERC recognized that in order for the Committee to make a recommendation for pertuzumab in combination with trastuzumab and chemotherapy in high-risk patient subgroups, other than those defined in the presently requested reimbursement criteria, a separate submission to pCODR would be required.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness analyses

The pCODR Economic Guidance Panel (EGP) assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years gained) and one cost-effectiveness analysis (clinical effects measured by life-years gained) comparing pertuzumab in combination with trastuzumab and chemotherapy against trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence, defined as either node-positive or hormone receptor–negative disease in the adjuvant setting.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were IDFS, OS, and utilities.

Costs considered in the analysis included those related to drug acquisition and administration, monitoring and follow-up medical resources, end-of-life care, and AEs.

Drug costs: Treatment costs of pertuzumab, trastuzumab, and chemotherapy

Pertuzumab costs $7.93 per mg. At the recommended dose of 840 mg (loading dose) administered as a 60-minute intravenous (IV) infusion, followed every three weeks thereafter by a dose of 420 mg (maintenance dose) administered over a period of 30 to 60 minutes, pertuzumab costs $6,657.10 (loading dose) and $3,328.55 (maintenance dose).

Trastuzumab costs $6.43 per mg. At the recommended dose of 8 mg/kg (loading dose) administered as an IV infusion, followed every three weeks thereafter by a dose of 6 mg/kg (maintenance dose), trastuzumab costs $3,466.55 (loading dose) and $2,599.92 (maintenance dose).

Cost of chemotherapy:

- 5-fluorouracil costs $0.03 per mg. At the recommended dose of 600 mg/m^2 IV every three weeks for three cycles, 5-fluorouracil costs $33.16 per treatment cycle.
- Epirubicin costs $4.01 per mg (small vial) and $3.90 per mg (large vial). At the recommended dose of 120 mg/m^2 IV every three weeks for three cycles, epirubicin costs $803.25 per treatment cycle.
- Doxorubicin costs $5.05 per mg (small vial) and $4.87 per mg (large vial). At the recommended dose of 50 mg/m^2 IV every three weeks for three cycles, doxorubicin costs $417.75 per treatment cycle. At the recommended dose of 60 mg/m^2 IV every three weeks for three cycles, doxorubicin costs $501.30 per treatment cycle. Note: Doxorubicin's recommended dose for the FAC (fluorouracil, adriamycin [doxorubicin], and cyclophosphamide) regimen is 50 mg/m^2; for the AC (Adriamycin [doxorubicin] and cyclophosphamide) regimen it is 60 mg/m^2.
- Cyclophosphamide costs $0.14 per mg (small vial) and $0.09 per mg (large vial). At the recommended dose of 600 mg/m^2 IV every three weeks for three cycles, cyclophosphamide costs $88.19 per treatment cycle.
- Paclitaxel costs $10.00 per mg (small vial) and $10.95 per mg (large vial). At the recommended dose of 80 mg/m^2 once weekly for 12 weeks, paclitaxel costs $1,373.89 per treatment cycle.
- Docetaxel costs $11.42 per mg (small vial) and $11.56 per mg (large vial). At the recommended dose of 100 mg/m^2 IV every three weeks for four cycles, docetaxel costs $1,961.83 per treatment cycle. At the recommended dose of 75 mg/m^2 IV every three weeks for four cycles, docetaxel costs $1,471.37 per treatment cycle. Note: Docetaxel's recommended dose for the TH (Taxotere [docetaxel] and Herceptin [trastuzumab]) regimen is 100 mg/m^2; for the TCH (Taxotere [docetaxel], carboplatin, and Herceptin [trastuzumab]) regimen it is 75 mg/m^2.
- Carboplatin costs $1.40 per mg (small vial) and $1.40 per mg (large vial). At the recommended dose of AUC 6 (area under the curve) every three weeks, carboplatin costs $909.84 per treatment cycle.

Cost-effectiveness estimates: No clinically meaningful benefit; ICERs cannot be determined

The submitter's base-case incremental cost-effectiveness ratios (ICERs) for the node-positive and hormone receptor–negative subgroups were lower than the EGP's reanalyzed ICERs. This was primarily due to the following factors:

- A shorter time horizon (40 years instead of 52 years): Given the age of 51 at diagnosis, a time horizon of 52 years seems highly unlikely for this patient population. The CGP supported a time horizon of 40 years.
- A shorter duration of treatment effect: The EGP assumed a treatment effect of four years (equivalent to median follow-up in the APHINITY trial), waning until seven years, instead of seven years, waning until 10 years, as assumed in the submitted base case.
- Assuming that "early metastatic recurrences" are all recurrences occurring less than 18 months of initiating adjuvant therapy (instead of less than 12 months of initiating adjuvant therapy): The CGP believe that recurrences less than 18 months would have similar poor prognosis as recurrences less than 12 months.
- Assuming the treatment mix in the metastatic setting according to the APHINITY trial (instead of according to expert opinion): The CGP felt that the treatment mix from the APHINITY trial was more relevant in the metastatic setting.
- For the node-positive subgroup only: The EGP chose a better-fitting parametric distribution for IDFS (exponential instead of log-logistic).

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter clarifying that the submitted base case assumed that early metastatic recurrences, which have poorer prognosis and thus are modelled differently than other metastatic recurrences in the

model, should be defined as all recurrences within 12 months of initiating adjuvant therapy. pERC discussed clarifications provided by the EGP in the pCODR Final Economic Guidance Report noting that the CGP reiterated that they would define early metastatic recurrences as all recurrences less than 18 months, as they believe that recurrences less than 18 months would have a similar poor prognosis as recurrences less than 12 months. Therefore, the EGP made no changes to the initial reanalyses.

According to the EGP's one-way scenario analyses, the factors that most influence the incremental effectiveness of pertuzumab, trastuzumab, and chemotherapy compared with trastuzumab and chemotherapy in the submitted base case include: (1) the duration of treatment effect and treatment mix in the metastatic setting for the node-positive subgroup, and (2) the duration of treatment effect and not adjusting the utilities for age for the hormone receptor-negative subgroup. The key cost drivers in the submitted base case include: (1) the treatment mix in the metastatic setting and the duration of treatment effect for the node-positive subgroup, and (2) the duration of treatment effect and the treatment mix in the metastatic setting for the hormone receptor-negative subgroup.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter suggesting that the main factors that influence the incremental effect in the submitted base case were the duration of effect and the treatment mix for the hormone receptor-negative subgroup. pERC discussed clarifications provided by the EGP in the pCODR Final Economic Guidance Report stating that the EGP maintains that according to the one-way scenario analyses performed for the hormone receptor-negative subgroup, removing the adjustment for age for the utilities from the submitted base case has a larger impact on the incremental effectiveness than changing assumptions around treatment mix. pERC agreed with the EGP that no changes had to be made to the pCODR Final Economic Guidance Report.

pERC noted that the estimates of incremental effect are largely based on a key clinical assumption that differences in the rate of IDFS can predict improvements in OS. However, given the Committee's lack of confidence in the clinical effect estimates for IDFS derived from the subgroup analyses and the uncertainty whether IDFS is a reliable surrogate outcome for OS, pERC was unsure that there is a clinically meaningful benefit. Therefore, pERC could not draw a conclusion on the cost-effectiveness and could not determine the ICERs of pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy for the adjuvant treatment of HER2-positive early breast cancer in patients who have node-positive or hormone receptor–negative disease.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter suggesting that it is possible to estimate an ICER. pERC discussed clarifications provided by the pCODR Economic Guidance Panel (EGP) in the pCODR Final Economic Guidance Report stating that the EGP agreed with pERC that the subgroup analyses were pre-specified but exploratory and, therefore, the trial was not designed to detect treatment effect differences based on subgroups. The EGP noted that there was a lack of evidence regarding a difference in treatment effect in each subgroup, which may impact the interpretation of the magnitude of incremental effectiveness, and the resulting ICER. In addition, the EGP stated that, if IDFS is not accepted as a meaningful surrogate for OS in this patient population by pERC, the results of the economic model are difficult to interpret as the model is dependent on the acceptance of this outcome. pERC agreed to uphold its initial position that it could not draw a conclusion on the cost-effectiveness and could not determine the incremental cost-effectiveness ratio (ICER) of pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy for the adjuvant treatment of HER2-positive early breast cancer in patients who have node-positive or hormone receptor–negative disease.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Substantial budget impact; pertuzumab available only in combination kit for this indication

pERC considered the feasibility of implementing a reimbursement recommendation for the pertuzumab combination for the adjuvant treatment of HER2-positive early breast cancer in patients who have node-positive or hormone receptor–negative disease. The Committee agreed with the pCODR Provincial Advisory Group that, for this submission, pertuzumab is only available in a package that includes both pertuzumab and trastuzumab (Perjeta-Herceptin Combo Pack) and is a barrier to implementation. Although pertuzumab is administered at a fixed dose, trastuzumab is administered based on weight. While

it is possible that excess trastuzumab can be used for other patients, the burden on inventory management resources would be substantial. pERC acknowledged feedback from the submitter that pertuzumab is available in Canada as a single vial. Making pertuzumab available on its own for the present indication, instead of being available only in a combination kit, would be preferred for implementation. In addition, pERC noted that pertuzumab is a high-cost drug and that the submitted Ontario-specific budget impact was substantial and likely underestimated. pERC acknowledged that, according to the EGP's reanalysis, the submitted incremental three-year budget impact (1) increased by about 14% if the market share was increased to 50%, 64%, and 75% in years 1, 2, and 3, and (2) increased by about 12.5% if the proportion of patients assumed to receive adjuvant treatment was increased by 10% from baseline. pERC concluded that the estimated substantial budget impact was a barrier to implementation.

Furthermore, pERC noted that for the absolute risk of avoiding one invasive disease event in three years, the numbers needed to treat are 112 for the overall population, 56 for the node-positive population, and 63 for the hormone receptor–negative population.

DRUG AND CONDITION INFORMATION

Drug Information	• Pertuzumab (Perjeta) is a recombinant humanized monoclonal antibody and is a first-in-class human epidermal growth factor receptor 2 (HER2) dimerization inhibitor.
Cancer Treated	• Adjuvant treatment of HER2-positive early breast cancer of patients with node-positive or hormone receptor-negative disease
Burden of Illness	• Breast cancer remains one of the most common malignancies affecting Canadian patients, with 26,300 new cases diagnosed in 2017. The majority of these cases represent early stage, potentially curable disease. A proportion of these breast cancer tumours (15% to 30%) are HER2-positive, which has been associated with poorer prognosis and more aggressive disease.
Current Standard Treatment	• Trastuzumab and chemotherapy
Limitations of Current Therapy	• Considerable side effects. Up to one in four HER2-positive patients with early breast cancer experience recurrence or death within 10 years of diagnosis.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Dr. Christopher Longo, Economist
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Dr. Maureen Trudeau, who was excluded from chairing and voting due to a conflict of interest.
- Dr. Anil Abraham Joy, Lauren Flay Charbonneau, and Carole McMahon, who were excluded from voting due to a conflict of interest.

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Economist
Valerie McDonald, Patient Member

Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Economist

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

- Dr. Maureen Trudeau, who was excluded from chairing and voting due to a conflict of interest.
- Dr. Anil Abraham Joy, Dr. Henry Conter, Lauren Flay Charbonneau who were excluded from voting due to a conflict of interest.
- Daryl Bell, Dr. Winson Cheung, Dr. Avram Denburg, Dr. Kelvin Chan, and Dr. Christine Kennedy who were not present for the meeting.

Avoidance of conflicts of interest

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

Information sources used

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

Consulting publicly disclosed information

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

Use of this Recommendation

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

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