pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The 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-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

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

Drug: Perjeta or Perjeta-Herceptin Combo Pack (Pertuzumab) **Submitted Funding Request:** In combination with trastuzumab and chemotherapy prior to surgery for the treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter or node positive) as part of a complete treatment regimen for early stage breast cancer	
Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: N/A	**Submission Date:** December 19, 2014
Initial Recommendation: April 30, 2015	**Final Recommendation:** July 16, 2015

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) does not recommend funding pertuzumab (Perjeta) in combination with trastuzumab and a taxane as neoadjuvant treatment for patients with HER2-positive primary operable or locally advanced/inflammatory breast cancer.

pERC made this recommendation because the Committee could not conclude that neoadjuvant treatment with pertuzumab, trastuzumab and docetaxel resulted in a net clinical benefit compared with trastuzumab and docetaxel for the group of patients requested by the submitter as pathological complete response has not been validated as a surrogate for either event-free survival or overall survival.

pERC considered that the use of pertuzumab, trastuzumab, and docetaxel partially aligned with patient values. Although pERC acknowledged that patients value additional treatment options, the Committee was not satisfied that the addition of pertuzumab to neoadjuvant treatment with trastuzumab and docetaxel addresses the key outcomes that patients have indicated they value such as prolongation of survival and prevention of disease recurrence.

pERC could not draw a conclusion on the cost-effectiveness of pertuzumab in combination with trastuzumab and a taxane in the neoadjuvant setting due to the uncertainty surrounding the incremental benefits used in the economic model.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Evidence Required to Establish Clinical Benefit
pERC noted that future trials of neoadjuvant breast cancer therapy should consider either event-free survival or overall survival as the primary endpoints and correlate these outcomes with pathological complete response.

SUMMARY OF pERC DELIBERATIONS

pERC noted that selected patients with human epidermal growth factor receptor-2 (HER2)-positive primary operable (Stage II) and locally advanced/inflammatory (Stage III) breast cancer are treated with neoadjuvant therapy with trastuzumab in combination with an anthracycline and a taxane in Canada. The goal of neoadjuvant treatment in women with locally advanced/inflammatory (Stage III) disease is to convert a patient with clinically inoperable disease to operable status, whereas in women with primary operable (Stage II) disease, the goal is to downstage the tumour in order to make breast conservation surgery possible in a woman who would otherwise require a mastectomy.

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

pERC deliberated upon the results of two randomized phase II trials, NeoSphere and TRYPHAENA. Given that the TRYPHAENA study included pertuzumab in all treatment arms, it was not considered further by the Committee in its deliberations regarding clinical benefit. The NeoSphere trial included four arms, of which the Committee noted that only two provided a relevant comparison: Arm B, pertuzumab, trastuzumab and docetaxel, and Arm A, trastuzumab and docetaxel. pERC noted that the primary outcome in the NeoSphere trial was pathological complete response (pCR) and that a statistically significant difference was demonstrated in favour of the pertuzumab, trastuzumab, and docetaxel arm compared with trastuzumab and docetaxel. pERC considered that although the pCR results were statistically significant, the NeoSphere trial was a proof-of-concept phase II study whose design allowed a higher probability than a phase III study for observing a difference in effect between treatment arms where no such difference exists. This decreased the Committee's confidence in the estimate of effect. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the Submitter based on an analysis at five years of the disease-free and progression-free survival from the phase II NeoSphere trial, which was suggestive of a benefit from adding pertuzumab to trastuzumab and docetaxel in the neoadjuvant setting. These data were previously available to pERC. The Committee noted that the NeoSphere trial did not demonstrate statistically significant differences in either disease-free or progression-free survival from the addition of pertuzumab to trastuzumab and docetaxel arm compared with the trastuzumab and docetaxel arm. pERC also noted the limitations of the design of the NeoSphere trial design, as previously discussed by the Committee. Therefore, pERC concluded that its lack of confidence in the estimate of effect was unchanged from the Initial Recommendation.

The Committee noted that the greatest uncertainty in the clinical benefit arose when determining if pCR is a validated surrogate for long-term outcomes such as event-free survival and overall survival. pERC considered evidence from a systematic review and meta-analysis investigating the relationship between pCR and long-term outcomes in trials of neoadjuvant treatment for breast cancer. pERC acknowledged that at the individual level, patients with breast cancer who receive neoadjuvant treatment and who obtain a pCR have longer event-free survival and overall survival than patients who do not obtain a pCR. However, the Committee noted that the meta-analysis indicated that differences in the frequency of pCR were not associated with improvements in event-free survival or overall survival at the trial level. That is, pCR cannot be reliably used in a trial to detect improvements in event-free survival or overall survival when comparing different treatments. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the Submitter regarding the relationship between pCR and long-term outcomes. pERC re-deliberated upon the differences between the individual-level (or responder) analysis and the trial-level analysis reported by Cortazar et al. pERC noted that while the meta-analysis demonstrated that a pCR in an individual patient is statistically associated with longer survival (i.e., individual-level analysis), it also demonstrated that, when comparing differences in the proportion of patients who achieve pCR between treatment arms across all of the included trials (i.e., trial-level analysis), there was no statistical association with differences in overall or event-free survival between treatment arms. pERC agreed with Cortazar et al that an association between pCR and overall or event-free survival needs to be demonstrated at both the individual level and the trial level in order to provide sufficient evidence to conclude that a causal relationship exists between pCR and overall or event-free survival. Therefore, based on the best available evidence, pERC could not conclude that a higher rate of

pCR in one arm of a randomized clinical trial comparing two neoadjuvant chemotherapies predicts for improved event-free or overall survival in that arm of the clinical trial.

pERC noted that the NeoALTTO phase III trial, which compared lapatinib to trastuzumab or to lapatinib plus trastuzumab, demonstrated similar results as the Cortazar meta-analysis, in that patients who achieved a pCR had longer event-free survival and overall survival compared to patients who did not achieve a pCR; however, the study did not provide evidence that an improvement in the frequency of pCR between treatment arms was associated with an improvement in event-free survival or overall survival. Therefore, based on the best available evidence, pERC could not conclude that pCR is a validated surrogate for either overall survival or event-free survival in trials of breast cancer conducted in the neoadjuvant setting. As such, pERC could not conclude that the neoadjuvant use of pertuzumab in combination with trastuzumab and docetaxel resulted in a net clinical benefit compared with neoadjuvant treatment with trastuzumab plus docetaxel. Upon reconsideration, the Submitter noted that the NOAH trial of neoadjuvant trastuzumab in combination with chemotherapy provided further evidence of the relationship between pCR and long-term outcomes given the similarities in the absolute increase in PCR rate between trastuzumab and pertuzumab in the metastatic and neoadjuvant settings. pERC re-deliberated upon the available evidence and considered the results of the NOAH trial; however, the Committee concluded that the Cortazar meta-analysis provided higher quality evidence than a single selected study. Therefore pERC was more confident of the Cortazar meta-analysis results.

Also upon reconsideration, pERC discussed feedback from the Submitter that the US FDA has approved the use of pertuzumab in the neoadjuvant setting. pERC noted that regulatory agencies, such as the US FDA, examine safety and efficacy, but have a different purpose than health technology assessment bodies. Whereas a regulatory agency needs to determine a minimum efficacy level and acceptable safety profile, health technology assessment 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. In addition, pERC noted that while the US FDA gave regulatory approval for pertuzumab in combination with trastuzumab and docetaxel as a neoadjuvant treatment in patients with breast cancer, the agency required a confirmatory phase III trial to further establish the efficacy, safety and long-term outcomes of the addition of pertuzumab. The Submitter also provided feedback that some clinical practice guidelines on breast cancer supported the neoadjuvant use of pertuzumab. pERC noted that there is a large difference of opinion within the clinical community with respect to the utility of pCR as an outcome in clinical trials in the neoadjuvant setting. This is highlighted by the opposing positions of the NCCN guidelines, which is in favour of the use of pertuzumab, and the European Society for Medical Oncology (ESMO), which does not recommend the addition of pertuzumab to trastuzumab and docetaxel.

Upon reconsideration of the Initial recommendation and in the context of the Submitter's feedback noted above, the Committee upheld its initial conclusion that pCR is not as yet a validated surrogate outcome for either event-free or overall survival in trials of breast cancer conducted in the neoadjuvant setting. Therefore, pERC could not conclude that the addition of pertuzumab to trastuzumab and docetaxel resulted in a net clinical benefit compared with trastuzumab and docetaxel alone in the neoadjuvant treatment of breast cancer.

pERC discussed input from one patient advocacy group and considered that the neoadjuvant use of pertuzumab partially aligned with patient values. While pERC acknowledged that neoadjuvant pertuzumab provides an additional treatment option, the Committee noted that the clinical benefit is highly uncertain. Patient advocacy group input indicated that patients value prolongation of life and reduction of disease recurrence. pERC was not satisfied that the differences in the rates of pCR observed between the pertuzumab, trastuzumab, and docetaxel arm compared with the trastuzumab and docetaxel arm in the NeoSphere trial would translate into improvements in event-free survival or overall survival that patients expected.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback received from the patient advocacy group that stated that patients value treatments with the potential to convert unresectable disease to resectable. pERC noted that this was not an objective of the NeoSphere trial and there were no data available on this outcome from this trial. In addition, pERC considered that the rate of conversion to breast-conserving surgery was similar in patients who received pertuzumab, trastuzumab and docetaxel compared with those who received trastuzumab and docetaxel alone. pERC acknowledged that individual patients who attain pCR have a higher probability of having longer event-free or overall survival; however, this was not demonstrated to be the case at the trial level and pERC also considered

that the best available evidence has not demonstrated that pCR can predict long-term outcomes in the neoadjuvant setting.

pERC deliberated on the cost-effectiveness of pertuzumab, trastuzumab and docetaxel compared with trastuzumab and docetaxel as neoadjuvant treatment for early-stage or locally advanced/inflammatory breast cancer. The Committee agreed with the pCODR Economic Guidance Panel's (EGP) assessment that the estimate of incremental effect was largely based on a key clinical assumption that differences in the rate of pCR can predict improvements in event-free survival and overall survival. Given the continued uncertainty surrounding the assumption that pCR is a surrogate for either event-free survival or overall survival, pERC could not accept that there is a net clinical benefit. Therefore, pERC could not determine the incremental cost-effectiveness ratio for pertuzumab, trastuzumab, and docetaxel compared with trastuzumab and docetaxel.

pERC noted input from the Provincial Advisory Group that potential barriers to implementation included the unknown long-term clinical benefits of the addition of pertuzumab to trastuzumab plus chemotherapy in the neoadjuvant setting and the high cost of pertuzumab.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from two patient advocacy groups (Canadian Breast Cancer Network)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group
- one patient advocacy group (Canadian Breast Cancer Network)
- the Submitter (Hoffmann-La Roche Limited)

The pERC Initial Recommendation was to not fund pertuzumab (Perjeta) in combination with trastuzumab and a taxane as neoadjuvant treatment for patients with HER2-positive primary operable or locally advanced/inflammatory breast cancer.

Feedback on the pERC Initial Recommendation indicated that pCODR's Provincial Advisory Group agreed with the Initial Recommendation, whereas the Submitter and patient advocacy group disagreed.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the effectiveness and safety of pertuzumab in combination with trastuzumab and chemotherapy in the neoadjuvant setting for the treatment of patients with human epidermal growth factor receptor-2 (HER2) positive locally advanced, inflammatory, or early stage breast cancer who have not received any previous cancer therapy for their disease.

Studies included: Two randomized phase II trials

The pCODR systematic review included two randomized phase II trials. The first study, NeoSphere (Gianni, 2012), was a four-arm, open-label trial that randomized patients with HER2-positive locally advanced, inflammatory, or primary operable breast cancer to trastuzumab plus docetaxel (Arm A, n=107); pertuzumab plus trastuzumab plus docetaxel (Arm B, n=107); pertuzumab plus trastuzumab (Arm C, n=107), or; pertuzumab plus docetaxel (Arm D, n=96). The primary endpoint of the study was pathological complete response (pCR). pERC noted that the trial was a proof-of-concept study and was designed with an alpha=0.20 for the comparisons of Arm A to Arm B, Arm A to Arm C, and Arm B to Arm D. The second study, TRYPHAENA (Schneeweiss, 2013), was a three-arm trial that randomized patients with HER2-positive primary operable, locally advanced or inflammatory breast cancer to pertuzumab and trastuzumab in cycles 1-6 plus FEC-5 (fluorouracil, epirubicin, cyclophosphamide) in cycles 1-3 and docetaxel in cycles 4-6 (Arm A, n=73); FEC-5 in cycles 1-3 followed by pertuzumab, trastuzumab, and docetaxel in cycles 4-6 (Arm B, n=75), or; pertuzumab, trastuzumab, docetaxel, and carboplatin in cycles 1-6 (Arm C, n=77). Pertuzumab and trastuzumab were administered according to the same doses as used in the NeoSphere study. The primary endpoint of the study was cardiac safety and no hypothesis testing was conducted. pERC noted that all arms in this study received pertuzumab and, therefore, it did not provide evidence of the comparative efficacy of pertuzumab in combination with trastuzumab and chemotherapy versus trastuzumab and chemotherapy without pertuzumab.

Patient populations: Majority with primary operable or locally advanced disease

In both studies, patient characteristics were generally balanced between arms.

NeoSphere study: Approximately 60% of patients in the study had primary operable disease, 30% had locally advanced disease, and <10% had inflammatory breast cancer. A little less than half of the patients in each arm had disease that was estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, or both. The median age of patients was 50 years in arms A and B, and 49 years in Arms C and D. The majority of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 in each arm (range, 83% to 94%), with the remaining patients having an ECOG performance status of 1.

TRYPHAENA study: Approximately 72% of patients in Arms A and B and 64% of patients in Arm C had primary operable disease, and approximately 37% of patients in Arms A and B and 31% of patients in Arm C had locally advanced or inflammatory disease. Approximately 53% of patients in Arm A, 47% in Arm B, and 51% in arm C had disease that was ER-positive or PR-positive. The median age was 49 years in Arms A and B and 50 years in Arm C. The majority of patients had an ECOG performance status of 0 in each arm (range, 88% to 90%), with the remaining patients having an ECOG performance status of 1.

Key efficacy results: Improvement in the rate of pCR; lack of survival data

The key efficacy outcome deliberated on by pERC was the rate of pCR.

NeoSphere: The rate of pCR (breast) was statistically significantly higher in the pertuzumab plus trastuzumab plus docetaxel group (Arm B) compared with the trastuzumab plus docetaxel group (45.8% versus [vs.] 29%, respectively; p=0.0141). The rate of pCR (breast and nodes [ypT0/is ypN0]) was 39.3% in Arm B and 21.5% in Arm A. In patients with T2-T3 tumours expected to undergo a mastectomy at baseline, the rate of conversion to breast conserving surgery was similar in both arms (Arm B, 23.2%; Arm A, 22.6%).

Upon reconsideration of the Initial Recommendation, pERC noted that the Submitter provided information from a five-year analysis of disease-free and progression-free survival from the NeoSphere trial, which was recently presented at ASCO that suggested that there was a benefit of adding pertuzumab to trastuzumab and docetaxel in the neoadjuvant setting. These data were previously available to pERC. The Committee again noted that the NeoSphere trial did not demonstrate statistically significant differences in either disease-free or progression-free survival between the pertuzumab, trastuzumab, and docetaxel arm compared with the trastuzumab and docetaxel arm. In addition, pERC noted that the NeoSphere trial had a randomized phase II design and, as such, had a small sample size which increases the probability of detecting an apparent difference in disease-free or progression-free survival when, in fact, no such difference existed.

TRYPHAENA: The rates of pCR (breast) in this study were similar in all three arms and were slightly higher than in the NeoSphere study (61.6% in Arm A, 57.3% in Arm B, and 66.2% in Arm C). The rate of pCR (breast and nodes [ypT0/is ypN0]) was 56.2% in Arm A, 54.7% in Arm B, and 63.6% in Arm C. The rate of conversion to breast conserving surgery was similar to that reported in the NeoSphere study (21.7% in Arm A, 16.7% in Arm B, and 27.0% in Arm C).

Quality of life: No data available

No data on quality of life were available for either the NeoSphere or the TRYPHAENA study.

Safety: Similar toxicity with or without pertuzumab

In the NeoSphere study, 12% of patients who received pertuzumab, trastuzumab and docetaxel (Arm B) and 14% who received trastuzumab and docetaxel (Arm A) experienced a grade 3 or higher adverse event. The rate of grade 3 or higher neutropenia was greater in the patient groups who received docetaxel (Arm A, 57%; Arm B, 45%; Arm D, 55%) than in the patient groups who did not receive docetaxel (Arm C, 1%). The other most common grade 3 or higher adverse events were febrile neutropenia (range 7% to 8% in docetaxel arms and none in the arm without docetaxel) and leukopenia (range 5% to 12% in the docetaxel arms and none in the arm without docetaxel). No significant decrease in the mean maximum left ventricular ejection fraction (LVEF) was detected when pertuzumab was added to trastuzumab and no patient experienced an LVEF decrease to less than 40% at any time during the study. During neoadjuvant treatment, no patients withdrew due to an adverse event in either the trastuzumab plus docetaxel arm (Arm A) or in the pertuzumab plus trastuzumab plus docetaxel arm (Arm B), while two patients in each of the remaining treatment arms did so.

In the TRYPHAENA study, neutropenia, febrile neutropenia, and leukopenia were the most commonly reported grade 3 or higher adverse events.

Outcomes: Insufficient evidence to support the validity of pCR as a surrogate for long-term outcomes

A systematic review and meta-analysis that assessed the relationship between pCR and long-term outcomes in breast cancer was considered by pERC (Cortazar, 2014). A total of 12 trials, with 11,955 patients, that examined the neoadjuvant treatment of breast cancer were included in the study. An association between pCR and event-free survival (EFS) and between pCR and overall survival was reported, at the individual level. The association was strongest in patients with total pCR (no invasive disease in the breast or nodes) and in patients with triple-negative breast cancer and in patients with HER2-positive, hormone-receptor negative breast cancer. However, at the trial level, pERC noted that no

association was demonstrated between increased frequency of pCR and improvements in either EFS or overall survival. pERC noted that the best available evidence could not validate pCR as a surrogate endpoint for improved event-free survival or overall survival.

Upon reconsideration, pERC discussed feedback from the Submitter expressing concern that while there is no conclusive evidence of a link between pCR and long-term outcomes at a trial level, that the meta-analysis by Cortazar et al provided evidence that individual patients who attain pCR have improved event-free survival or overall survival. pERC discussed the differences between the individual-level analysis and the trial-level analysis reported by Cortazar et al. pERC acknowledged that while the Cortazar meta-analysis demonstrated an association between attainment of pCR and longer event-free and overall survival at the individual level, a pooled analysis across all trials that compared the size of the effect of pCR, between treatment arms of the pooled trials, with the effect size of overall survival and event-free survival, between treatment arms of the pooled trials, did not demonstrate that the rate of pCR within a trial predicts long-term outcomes. pERC agreed with Cortazar et al that an association between pCR and overall or event-free survival needs to be demonstrated at both the individual level and the trial level in order to provide sufficient evidence to conclude that a causal relationship exists between pCR and overall or event-free survival. While the meta-analysis demonstrated that a pCR in an individual patient is associated with longer survival, there is insufficient evidence to demonstrate a causal relationship between pCR and either event-free survival or overall survival given the lack of an association between differences in the rate of pCR between treatment arms and differences in survival between treatment arms in a meta-analysis of trials conducted in the neoadjuvant breast cancer setting.

The NeoALTTO study was discussed as relevant contextual information. NeoALTTO was a randomized phase III trial in which 455 women with HER2-positive early breast cancer were randomized 1:1:1 to receive either lapatinib, trastuzumab, or lapatinib plus trastuzumab, for six weeks followed by an additional 12 weeks in combination with weekly paclitaxel. Patients then underwent definitive surgery followed by 3 cycles of FEC, followed by 34 weeks of the assigned anti-HER2 regimen. This study was published in 2014, after the meta-analysis by Cortazar et al was conducted. The primary endpoint was pCR and secondary endpoints included event-free survival, overall survival, and the association between pCR and event-free survival or overall survival (30 weeks after randomization). No statistically significant differences in 3-year event-free survival (median follow-up 3.77 years) or 3-year overall survival (median follow-up 3.84 years) were demonstrated between the three treatment arms; however, the trial was not powered to detect differences in either of those outcomes. The analysis of an association between patients who achieved pCR compared with those who did not demonstrated a statistically significant improvement in 3-year event-free survival (HR 0.38, 95% CI 0.22 to 0.63; p0.0003) and in 3-year overall survival (HR 0.35, 95% CI 0.15 to 0.70; p=0.005). pERC noted that, the NeoALTTO study demonstrated that patients with a pCR had longer overall survival and event-free survival compared with patients without a pCR similar to the Cortazar meta-analysis; however, the trial did not provide evidence that an improvement in the *frequency* of pCR in one arm of a trial is associated with an improvement in event-free survival or overall survival.

Upon reconsideration, pERC discussed feedback from the Submitter that the NOAH trial was more contextually relevant than the NeoALTTO trial and that it provided further evidence of the relationship between pCR and long-term outcomes given the similarities in the data between trastuzumab and pertuzumab in the metastatic and neoadjuvant settings. pERC noted that while the NOAH trial, which compared chemotherapy with anti-HER2 therapy to chemotherapy alone, demonstrated both improved rates of pCR and improved event-free survival in the neoadjuvant setting, the Committee also noted the availability of higher quality evidence in the form of the meta-analysis reported by Cortazar et al. pERC could not conclude, given the totality of evidence, that pCR is validated as a surrogate outcome for either event-free or overall survival.

Comparator information: Neoadjuvant trastuzumab in combination with an anthracycline and a taxane

In Canada, women with HER2-positive primary operable, locally advanced or inflammatory breast cancer, when treated in the neoadjuvant setting, receive trastuzumab in combination with an anthracycline and a taxane.

Need: Additional treatment options are required in patients with early-stage and locally advanced/inflammatory breast cancer

The 5-year disease-free survival (DFS) for women with primary operable node-negative disease treated in trials of adjuvant trastuzumab is more than 90%. In patients with locally advanced or inflammatory breast

cancer, long-term outcomes are available from the NOAH study, which compared neoadjuvant chemotherapy with or without trastuzumab. The five-year EFS was 58% (95% confidence interval [CI], 48% to 66%) in the trastuzumab-containing arm. pERC noted that the goal of neoadjuvant treatment for patients with primary operable disease (Stage II) is to make breast conservation surgery possible in a woman who would otherwise require a mastectomy, whereas in patients with locally advanced/inflammatory disease (Stage III), the goal is to convert inoperable disease to operable status.

PATIENT-BASED VALUES

Values of patients with breast cancer: Treatment options that reduce recurrence and prolong survival

Input from one patient advocacy group indicated that patients with breast cancer who would be candidates for neoadjuvant treatment value prolonged life expectancy and prevention of disease recurrence without significantly increasing side effects.

pERC also noted that there is a considerable financial impact on caregivers as they need to take time off work and incur additional costs associated with the disease that are not covered under public or private health plans. In addition, caregivers often experience increased anxiety and stress due to the additional responsibilities placed upon them.

Upon reconsideration, pERC discussed feedback received from a patient advocacy group that expressed concern that pERC had not fully considered all values that are important to patients. The patient advocacy group noted that patients value treatments that have the potential to convert unresectable disease to resectable. pERC noted that this was not an outcome measured in the NeoSphere trial and, therefore, no data on this outcome were available to inform this patient value. In addition, pERC considered that the rate of conversion of patients to breast-conserving surgery was similar in patients who received pertuzumab, trastuzumab and docetaxel compared with those who received trastuzumab and docetaxel. pERC acknowledged that for individual patients who attain pCR, their probability of having longer event-free or overall survival is increased; however, pERC also considered that the best available evidence has not demonstrated that differences in the rate of pCR between treatment arms in a trial predict for differences in event-free or overall survival. Therefore, given that the ability of pCR to predict long-term outcomes has not been demonstrated, the Committee concluded that the neoadjuvant use of pertuzumab, trastuzumab and docetaxel in patients with breast cancer only partially aligns with patient values.

Patient values on treatment: Willing to tolerate side effects for prolongation of life; Limited information on patients' experiences with pertuzumab

pERC noted that patients felt that the greatest side effects of treatment were due to the chemotherapy component of their treatment. Patients indicated that they were willing to tolerate the additional side effects of pertuzumab due to the potential benefit for prolonged life. pERC also noted that the input from the patient advocacy group provided very limited information on patients' experiences with pertuzumab. The number of interviewees included in the key informant interviews was unclear; however, the Committee noted that at most three patients were interviewed, with one having previously received pertuzumab. pERC noted that the patient who had experience with pertuzumab indicated that the side effects of pertuzumab were less severe than chemotherapy with docetaxel. Patients also indicated that they felt that the side effects were tolerable given the potential benefit.

Economic model submitted: Cost-utility analyses

The pCODR Economic Guidance Panel (EGP) assessed two cost-utility analyses of neoadjuvant treatment for patients with primary operable or locally advanced/inflammatory breast cancer: one main analysis based on the NeoSphere study that compared a neoadjuvant regimen of pertuzumab, trastuzumab and docetaxel to trastuzumab and docetaxel; and a second analysis, based on the TRYPHAENA study, where a neoadjuvant regimen of pertuzumab, trastuzumab, docetaxel, and carboplatin was compared with a hypothetical neoadjuvant regimen consisting of trastuzumab, docetaxel, and carboplatin, which was based on the efficacy observed in the non-pertuzumab arm of the NeoSphere study.

Basis of the economic model: Clinical and economic inputs

Costs considered in the analysis included the cost of treatment and administration, the costs associated with Grade 3 or higher adverse events, and the average cost of subsequent therapy.

The key clinical outcomes considered in the analysis were improvements in pCR that were extrapolated to estimate the extension of overall survival and improvements in health-related quality of life.

Drug costs: Key drivers included drug cost, the effect of treatment as measured by pCR, cost of treatment post-progression, and duration of survival

At the list price, pertuzumab costs $3,535.00 per 420 mg/14 mL vial. At the recommended loading dose of 840 mg, cycle 1 costs, $294.58 per day and $8,248.33 per 28-day course. For the subsequent cycles, at the recommended dose of 420 mg, the cost per day is $168.33 and $4,713.33 per 28-day course. At the submitted confidential price, pertuzumab costs $[redacted] per 420 mg/14 mL vial. *(The cost of pertuzumab is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the pCODR Disclosure of Information Guidelines.)*

At the list price, trastuzumab costs $2,700.00 per 440 mg vial. Assuming an average weight of 70 kg, at the recommended loading dose of 8 mg/kg, the average daily cost for cycle 1 is $153.29, or $4,292.12 per 28-day course. For subsequent cycles, at the recommended dose of 6 mg/kg, the average daily cost is $122.63, and $3,433.70 per 28-day course.

At the list price, docetaxel costs $3.43/mg. Assuming a body surface area of 1.7m^2, the cost of the recommended initial dose of docetaxel (75 mg/m^2) is $20.81 per day, and $582.59 per 28-day course and at the escalation dose (100 mg/m^2) is $27.74 per day, and $776.79 per 28-day course. The Submitter used a cost of docetaxel of $11.42/mg and assumed a body surface area of 1.78m^2.

Clinical effect estimates: Key drivers were effect of treatment as measured by pCR, assumption that pCR predicts duration of survival, and utilities

The EGP's best estimate of the extra clinical effect of pertuzumab plus trastuzumab plus docetaxel was between 0.310 and 0.385 quality adjusted life-years (QALYs). The factors found to most influence the incremental effectiveness were effectiveness of treatment as measured by pCR and the predicted duration of survival, as well as the utilities associated with each health state. The EGP noted that their best estimate relies on the assumption that an improvement in pCR can be translated into an improvement in overall survival and progression-free survival. pERC noted that there is considerable uncertainty regarding the use of pCR as a validated surrogate for long-term outcomes such as overall survival or progression-free survival.

Cost-effectiveness estimates: pERC unable to determine the incremental cost-effectiveness ratio

pERC noted that the range of estimates of incremental cost-effectiveness provided by the EGP included the manufacturer's point estimate. pERC noted that the EGP's best estimate relied on the assumption that pCR is a validated surrogate for long-term clinical outcomes and that improvements in the rate of pCR predict for improvements in progression-free survival or overall survival in the neoadjuvant setting. As pERC was not satisfied that pCR is a validated surrogate for long-term outcomes, the Committee was unable to use the submitted model to determine the incremental cost-effectiveness ratio.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Cost of pertuzumab and potential for indication creep

pERC noted that the potential budget impact would be affected by the cost of pertuzumab, the size of the population of interest (i.e., whether all patients with primary operable disease are included in the recommendation as opposed to just those with Stage IIB), the proportion of HER2-positive patients that receive neoadjuvant therapy, and the number of cycles of pertuzumab treatment.

The submitted BIA had several limitations including the lack of province-specific epidemiological inputs, the absence of the impact of introducing neoadjuvant pertuzumab on the cost of treatment at disease relapse, and the absence of an assumption on future generic substitution.

DRUG AND CONDITION INFORMATION

Drug Information	• A recombinant humanized monoclonal antibody that inhibits dimerization of HER2 with other HER receptors (HER3, HER1, and HER4) • 420 mg vial • Recommended initial dosage is 840 mg administered IV as a 60-minute infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over 30-60 minutes. Duration is recommended for 4 to 6 cycles.
Cancer Treated	• HER2-positive, locally advanced/inflammatory or early stage breast cancer (>2 cm in diameter or node positive)
Burden of Illness	• Breast cancer is the most common cancer in women and the 2nd most common cause of cancer mortality of Canadian women • Approximately 15-20% of all breast cancers are HER2-positive, resulting in a more aggressive clinical phenotype and a poorer prognosis.
Current Standard Treatment	• Anti-HER2 treatment (trastuzumab) in combination with anthracycline- or taxane-based chemotherapy as neoadjuvant treatment prior to surgery
Limitations of Current Therapy	• Women with node-negative disease have a more favourable prognosis while nearly half of women with node-positive disease (Stage IIB) or locally advanced/inflammatory disease (Stage III) will experience an event at 5 years following neoadjuvant treatment

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Tallal Younis, Oncologist
Dr. Kelvin Chan, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Drs. Allan Grill, Paul Hoskins, Tallal Younis, and Kelvin Chan who were not present for the meeting
- Drs. Bill Evans, Maureen Trudeau, Jo Nanson, and Carole McMahon who were excluded from voting due to a conflict of interest

All members participated in deliberations and voting on the final recommendation except:

- Drs. Scott Berry, Allan Grill, and Kelvin Chan who were not present for the meeting
- Dr. Bill Evans, Dr. Maureen Trudeau, Jo Nanson, and Carole McMahon who were excluded from voting due to a conflict of interest

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee 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 (Perjeta) for neoadjuvant breast cancer, through their declarations, seven members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, and four of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee 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 their 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*. Hoffmann-La Roche, as the primary data owner, did not agree to the disclosure of some clinical information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers 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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