PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pertuzumab (Perjeta) Neoadjuvant Breast Cancer

July 16, 2015

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Hoffmann-La Roche Limited** compared the addition of pertuzumab (Perjeta) to a 4-cycle neoadjuvant treatment regimen containing trastuzumab and docetaxel versus a neoadjuvant regimen with trastuzumab and docetaxel only for patients with HER2-positive, locally advanced, inflammatory or early stage (>2 cm in diameter or node positive) breast cancer. Pertuzumab is administered intravenously at a loading dose of 840mg followed every three weeks with a maintenance dose of 420mg. Trastuzumab is administered intravenously at a loading dose of 8mg/kg, followed every three weeks with a maintenance dose of 6mg/kg. Docetaxel is also administered intravenously with a dose of 75mg/m^2 escalating up to 100mg/m^2 given every three weeks. Two cost-utility analyses were submitted; one main analysis based on the randomized, multicentre, international, open-label phase II clinical trial (the *NeoSphere* trial) and one additional analysis using evidence from a randomized, multicentre, international, open-label phase II clinical trial (the *TRYPHAENA* trial) where a hypothetical comparator arm based on the efficacy observed in the NeoSphere trial has been added. The intervention in the additional analysis was assumed to be comprised of a 6-cycle neoadjuvant regimen including pertuzumab, trastuzumab, docetaxel and carboplatin. The hypothetical comparator was a 6-cycle neoadjuvant regimen including trastuzumab, docetaxel and carboplatin. This hypothetical arm was created since all arms in the TRYPHAENA trial were exposed to pertuzumab. The EGP relied on the results of the main analysis because the analysis based on the TRYPHAENA trial made extensive assumptions that were difficult to validate. The submitter used estimates from two studies (the Kim et al and the Caltazar et al studies) to extrapolate the treatment effect on pCR to improvements on event-free and overall survival.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. Current standard of care in first line treatment includes neoadjuvant therapy with trastuzumab and docetaxel. Modifications in the main analysis tried to capture the uncertainty around the model time horizon, comparative efficacy measured in pathological complete response (pCR), average cost of subsequent therapy of relapsed patients and utility for event free patients.

The patient advocacy group considered the following factors as important in the review of pertuzumab, which are relevant to the economic analysis: reduction in the risk of recurrence, disease progression and improvement in overall survival. The patient advocacy group also stressed the importance of not significantly increasing the impact of the disease on issues such as fatigue, pain and nausea. Finally the patient advocacy groups also mentioned the economic burden extending to the family and the caregivers with respect to time-off work costs. However, although time off work and caregiver burden are important aspects, according to pCODR's guidelines the health system perspective should be followed by the submitter, which does not include the effect of the intervention to productivity losses. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for pertuzumab, and which are relevant to the economic analysis: uncertainty around the long-term clinical benefits, exact population to benefit from the addition of pertuzumab, potential re-use in the adjuvant setting and the high cost of pertuzumab.

At the disclosable price, pertuzumab costs $3,535 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, or $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, or $582.59 per 28-day course and at the escalation dose (100 mg/m^2) is $27.74 per day, or $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.

1.2 Summary of Results

The CGP has identified that the population that is more likely to benefit from the addition of pertuzumab in the neoadjuvant therapy with trastuzumab and docetaxel is patients with HER-2 positive node positive (Stage IIB) and locally advanced/inflammatory (Stage III) breast cancer. Given the absence of subpopulation data for this population the EGR assumed that the effectiveness identified in the population of the NeoSphere trial is representative of the subpopulation indicated by the CGP. This is a conservative approach and may underestimate the incremental effect, and therefore may overestimate the incremental cost effectiveness ratio in the population recommended by the CGP.

The EGP's best estimates rely on the assumption that an improvement in pCR can be translated into an improvement in overall and progression free survival.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) for neoadjuvant therapy with pertuzumab, trastuzumab and docetaxel versus trastuzumab and docetaxel alone was between $17,103 and $27,550 per quality-adjusted life year.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- The extra cost associated with pertuzumab, trastuzumab and docetaxel is between 6,585 and $8,550 (ΔC). The main factors were the cost of pertuzumab treatment, the effect of treatment as measured by pathological complete response (pCR), cost of treatment post progression and duration of survival.
- The extra clinical effect associated with pertuzumab, trastuzumab and docetaxel is between 0.31 and 0.385 QALYs (ΔE). The main factors were the pCR treatment effectiveness, the assumption around the duration of survival and the utilities associated with each health state

The EGP based these estimates on the model submitted by Hoffmann-La Roche Limited and reanalyses conducted by the EGP.

One of the assumptions made in the submitted model suggested that all patients that died within the first 10 years in the model, regardless of whether they experienced a relapse or not, would receive post-relapse therapy. The EGP believed that this assumption is unrealistic and inconsistent with the rest of the model assumptions. Instead the EGP assumed that only relapsed patients or patients that died because of the disease would be receiving post-relapse treatment.

Also, the submitter assumed two lines of post-relapse treatment: first line was pertuzumab, trastuzumab and docetaxel OR trastuzumab and docetaxel. Second line was trastuzumab emtansine OR capecitabine plus trastuzumab. The EGP made modifications to the cost assumed by the submitter for first line post-relapse treatment with pertuzumab, trastuzumab and docetaxel. This was done so that the cost is in accordance with estimates previously used by pCODR and because the EGP felt that there was a substantial risk of double counting. This estimate included the cost of first line treatment with pertuzumab, trastuzumab and docetaxel from treatment initiation until second relapse. After making these two changes in the submitted model the extra cost of neoadjuvant therapy with pertuzumab, trastuzumab and docetaxel was estimated at $8,550, which slightly increased the estimated incremental cost-effectiveness ratio.

The CGP also suggested that the stage IIB and III breast cancer patients and in particular those that are hormone receptor negative are likely to benefit more from the addition of pertuzumab in the neoadjuvant therapy, although it should not be restricted to this population only. For that reason and by using estimates from the NeoSphere trial, we conducted a subgroup analysis focusing on the hormone receptor negative breast cancer patients. In this subpopulation, the extra clinical effect of neoadjuvant chemotherapy with pertuzumab trastuzumab and docetaxel is 0.5 (ΔE_1) and the extra cost is $3,918, which decreases the estimated incremental cost-effectiveness ratio.

A systematic review and meta-analysis of breast cancer RCTs by Cortazar et al identified that a significant association exists between pCR and extended overall and progression free survival. However, an increase in the *frequency* of pCR was not found to be statistically associated with an increase in progression-free or overall survival. Estimates from this study were used in a scenario analysis by the submitter to extrapolate from pCR to overall and progression-free survival. However, the overall population in the systematic review originated from studies that included patients with different types of breast cancer (e.g. both HER2-positive and HER2-negative patients). The EGP conducted a sensitivity analysis where the estimates of relative difference in overall and progression-free survival between pCR and no pCR patients were coming from a subpopulation of the Cortazar et al study. This subpopulation was closer to the population of interest in this submission (i.e. HER2 positive breast cancer). Based on that reanalysis the extra clinical effect of neoadjuvant chemotherapy with pertuzumab trastuzumab and docetaxel is 0.385 and the extra cost is $6,585, which decreases the estimated incremental cost-effectiveness ratio.

The EGPs estimates were on average similar but more uncertain than the submitted estimates for the overall population.

The EGPs estimates were more favourable to the submitted estimates for the HER2 positive hormone negative population.

All EGP estimates rely on the assumption that an improvement in pCR can be translated into an improvement in overall and progression free survival.

Two analyses were submitted by Hoffmann-La Roche Limited.

The main economic analysis was based on the NeoSphere trial. According to this economic analysis when neoadjuvant therapy with 4 cycles of pertuzumab, trastuzumab and docetaxel is compared to 4 cycles of trastuzumab and docetaxel alone:

- The extra cost of pertuzumab, trastuzumab and docetaxel is $7,879 (ΔC). Costs considered in the analysis included cost of treatment, average cost of subsequent therapy and administration costs.
- The extra clinical effect of pertuzumab, trastuzumab and docetaxel is 0.333 life years or 0.310 quality-adjusted life years (QALYs) (ΔE). The clinical effect considered in the analysis was based on improvements in pCR that were extrapolated to estimate the extension of survival, and improvements in health-related quality of life.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $25,388/QALY

The additional economic analysis was based on the TRYPHAENA trial. Since in this trial patients in all arms were exposed to pertuzumab, the additional economic analysis compared neoadjuvant therapy with 6 cycles of pertuzumab, trastuzumab, carboplatin and docetaxel to a hypothetical arm including neoadjuvant therapy with 6 cycles of trastuzumab, carboplatin and docetaxel alone:

- The extra cost of pertuzumab, trastuzumab carboplatin and docetaxel is $14,337 (ΔC). Costs considered in the analysis included cost of treatment, average cost of subsequent therapy and administration costs.
- The extra clinical effect of pertuzumab, trastuzumab, carboplatin and docetaxel is 0.333 life years or 0.310 quality-adjusted life years (QALYs) (ΔE). The clinical effect considered in the analysis was based on improvements in pCR that were extrapolated to estimate the extension of survival, as well as improvements in health-related quality of life.

The Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) in the additional economic analysis was $46,196/QALY

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The EGP estimates were on average similar but more uncertain than those reported by the Submitter for the overall population. Both the submitter and the EGP estimates are based on the assumption that an improvement in pCR can be translated into an improvement in overall and progression free survival.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Factors raised by the patient advocacy group as important, such as the difference in overall and progression free survival as well as aspects related to quality of life and adverse events were adequately addressed by the submitted model. Issues associated with out-of pocket expenditure or time off work as well as the (economic) burden on caregivers were not addressed as economic analyses submitted take a health system perspective and therefore do not include these costs in their analyses.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Yes the design and the structure of the model is adequate, given the type of data currently available for the treatment alternatives.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

The most important assumption made by the submitter in the economic model is that pCR can be considered as a surrogate endpoint for overall and progression free survival. A systematic review and patient-level meta-analysis by Cortazar et al identified a strong relation between pCR and overall and progression free survival. However, a *change* in the frequency of pCR due to treatment was not found to be associated with a *change* in overall or progression free survival. The reason of the absence of a statistically significant relation was attributed to the small study-level relative survival effects observed in the studies included in the Cortazar et al. meta-analysis. However the meta-analysis of Cortazar et al suggests that the prognostic value of pCR is more likely to be higher in populations with a higher risk of relapse.

The EGP has considered these limitations and conducted a number of sensitivity analyses around the estimates of overall and progression free survival. Interpretation of the findings from this submission should be done in light of the uncertainty associated with this projection from pCR to overall and progression free survival.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

The estimates of clinical effect and costs used by the submitter were similar to the ones used by the EGP. Given the absence of overall and progression free survival data, this is the most accurate published estimates of effectiveness. However, estimates of overall and progression free survival effect should be collected when available from the NeoSphere trial. In addition information on the link between pCR and overall/progression-free survival for the CGP recommended population (HER2-positive, stage IIB, III breast cancer patients) would provide a more accurate estimate of cost-effectiveness.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The submitter provided a budget impact analysis that forecasts the absolute costs following market introduction of pertuzumab. The factors that strongly affect the budget impact analysis were: the cost of pertuzumab, the decision on the population of interest, the proportion of HER2 positive patients and early HER2 positive patients that receive neoadjuvant therapy and the number of cycles of pertuzumab treatment.

What are the key limitations in the submitted budget impact analysis?

Key limitations in the budget impact analysis includes the lack of province specific epidemiologic estimates. In addition, given that this recommendation focuses on a patient subpopulation of those that NeoSphere focused it is important to be noted that the budget impact might vary if significant indication creep occurs.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

The economic analysis could be improved with data linking pCR with overall and progression free survival that are more tailored to the (sub)population of interest. In addition data on overall and progression free survival from the NeoSphere trial would be necessary for an accurate estimate of treatment effectiveness. Although not necessary for this review process incorporating productivity loss and caregiver burden within the decision model could help answer some of the patient advocacy concerns.

Is there economic research that could be conducted in the future that would provide valuable information related to pertuzumab for HER2+, locally advanced, inflammatory or early breast cancer population?

The extrapolation of current results of the NeoSphere trial on pCR to overall and progression free survival need to be confirmed by long-term phase III randomized trials such as the APHINITY trial. Such evidence will allow more robust conclusions with respect to the magnitude of the benefit and the target population receiving this benefit.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Breast Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of Pertuzumab for the Neoadjuvant treatment of breast cancer. A full assessment of the clinical evidence of Pertuzumab for the Neoadjuvant treatment of breast cancer is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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