



pan-Canadian Oncology Drug Review Final Economic Guidance Report

Lapatinib (Tykerb) with Letrozole for Metastatic Breast Cancer

July 5, 2013

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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 <i>pCODR Disclosure of Information Guidelines</i> , this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.	
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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis submitted to pCODR by GlaxoSmithKline Canada Inc. compared lapatinib plus letrozole to a number of comparators (letrozole-only, trastuzumab plus anastrozole and anastrozole only) for post menopausal women with hormone receptor positive and HER-2 positive metastatic breast cancer. Analysis reflects a subset of the EGF30008 phase 3 trial population from the Johnson (2009) study. Lapatinib and letrozole are both administered orally. The comparison with trastuzumab + anastrozole is based on an indirect comparison with Study EGF30008. Further details on the indirect comparison can be found in the Supplemental Issues section of the Clinical Guidance Report.

According to the pCODR Clinical Guidance Panel (CGP), these comparisons are valid. The Clinical Guidance Panel considered trastuzumab + anastrozole to be a comparator in this patient population.

Patient advocacy group input was not provided for the lapatinib (Tykerb) review; however, input from other relevant pCODR reviews of breast cancer treatments was used to inform the review.

Patient Advocacy Group Input considered the following factors important in the review of lapatinib, which are relevant to the economic analysis: access to treatments that could delay progression and extend life expectancy. Patients also felt it important to have manageable side effect profiles and maintain quality of life and lifestyle, but would be willing to accept toxicities for survival benefit.

A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

The pCODR Provincial Advisory Group (PAG) considered that the following factors would be important to consider if implementing a funding recommendation for lapatinib (Tykerb) + letrozole, and which are relevant to the economic analysis:

- Relevance as first line therapy.
- Cost relative to other alternate therapies.
- Indication creep
- Increased clinic visits

A full summary of the Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

At the list price, lapatinib (Tykerb) costs \$23.50 per 250 mg tablet and letrozole costs \$1.38 per 2.5mg tablet. The recommended dose of lapatinib is 1500 mg qd po and at the recommended dose, the average daily cost of lapatinib is \$141 and the average cost per-28 day course is \$3948. The recommended dose of letrozole is 2.5mg qd po and at the recommended dose, the average daily cost of letrozole is \$1.38 and the average cost per-28 day course is \$38.58.

Trastuzumab is available as 440 mg/vial at a cost of \$2698 per vial and anastrozole is available as a 1mg tablet at a cost of \$1.27. At the recommended dose of 6mg/kg every 3 weeks, the average cost of trastuzumab is \$90 per day and the average cost per 28-day course is \$2575. For the recommended loading dose of 8mg/kg, the average cost per day is

\$215 and the average cost per 28-day course is \$6009. At the recommended dose letrozole costs \$1.27 per day and the average cost per-28 day course is \$35.64.

1.2 Summary of Results

EGP and submitted estimates for the lapatinib + letrozole compared to placebo + letrozole:

The Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio is \$274,261 per quality-adjusted life year (QALY), when lapatinib (Tykerb) + letrozole was compared to letrozole alone for post menopausal women with hormone receptor positive and HER-2 positive metastatic breast cancer. This estimate is based on reanalyses conducted by the Economic Guidance Panel and using the model submitted by GSK Inc.

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

- extra cost (ΔC) of lapatinib+letrozole is \$59,838. Costs included drug costs and healthcare costs associated with routine follow-up for patients receiving active treatment, disease progression, routine health care resources involved in best supportive care and death. Costs associated with management of adverse events were also considered.
- extra clinical effect (ΔE) of lapatinib+letrozole is 0.218 QALYs. The biggest influence on QALYs was the estimate of extended progression free survival.

According to the economic analysis that was submitted by the manufacturer, when lapatinib (Tykerb) + letrozole was compared to letrozole alone in post menopausal women with hormone receptor positive and HER-2 positive metastatic breast cancer:

- The extra cost (ΔC) of lapatinib+letrozole is \$67,029 from the health care system perspective. The main contributor to increased cost is the cost of lapatinib.
- The extra clinical effect (ΔE) of lapatinib+letrozole is 0.440 QALYs. This was largely driven by the assumptions inherent in the model relating to projected longer PFS gains and greater post progression survival for lapatinib+letrozole.

So, the Submitter estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was \$152,344 per QALY for lapatinib+letrozole versus letrozole alone from the health care system perspective,

EGP and submitted estimates for the lapatinib + letrozole compared to trastuzumab + anastrozole:

The Economic Guidance Panel estimates that lapatinib (Tykerb) + letrozole is dominated by trastuzumab+anastrozole in that trastuzumab+anastrozole is equally effective but less costly than lapatinib+letrozole. This estimate is based on reanalyses conducted by the Economic Guidance Panel and using the model submitted by GSK Inc. Given the lack of head to head comparison data and the heterogeneity of the patient population in the indirect comparison, a definitive conclusion could not be made on the comparative cost effectiveness of lapatinib+letrozole compared to trastuzumab+anastrozole.

The result was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The **Economic Guidance Panel's** estimate is based on:

- An extra cost (ΔC) of lapatinib+letrozole of \$2,536.
- No increase in clinical effect (ΔE) when compared to trastuzumab+anastrozole.

According to the economic analysis that was submitted by the manufacturer, when lapatinib (Tykerb) + letrozole was compared to trastuzumab+anastrozole in post menopausal women with hormone receptor positive and HER-2 positive metastatic breast cancer:

- The extra cost (ΔC) of lapatinib+letrozole is \$5,805 from the health care system perspective.
- The extra clinical effect (ΔE) of lapatinib+letrozole is 0.236 QALYs. This was largely driven by the assumptions relating to improved time pre progression and post progression with lapatinib+letrozole.

So, the Submitter estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was \$24,561 per QALY from the health care system perspective.

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 key reasons are as follows:

- The manufacturer's use of a partitioned survival model which results in a greater post progression survival for lapatinib+letrozole than letrozole alone. As a result, the manufacturer's model showed a [REDACTED] month improvement in overall survival ([REDACTED] months vs. [REDACTED] months). The randomized study did not show a statistically significant improvement in overall survival (33.3 months vs. 32.3 months, respectively). As an alternate and more conservative approach, the EGP conducted a reanalysis using a traditional Markov model which replicates the median overall survival for letrozole only from the EGF30008 trial of 32.3 months. This was conducted through assuming an exponential survival function with respect to survival post progression. *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)*
- The manufacturer's use of a HR for progression free survival of [REDACTED] rather than 0.71 which was the estimate from the randomized controlled clinical trial. The estimate of 0.71 was based on the main end-point of the study for the HER-2 positive subgroup and calculated by stratified log-rank test, while [REDACTED] was based on a multivariable proportional hazard model. The unadjusted HR by stratified log-rank test for PFS in the HER-2 positive subgroup was the primary endpoint, while the multivariable proportional hazard model was built to assess the impact of baseline prognostic factors. As an alternate approach, the EGP conducted its reanalysis by assuming a HR for PFS of 0.71 for letrozole+lapatinib versus letrozole alone. *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)*

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- The manufacturer's assumption that lapatinib+letrozole has improved PFS over trastuzumab+anastrozole. This was based on an indirect comparison and the assumption that the relative effectiveness of letrozole versus tamoxifen and anastrozole versus tamoxifen is similar in HER2(+) and HER2(-) patients. The EGP conducted the reanalysis by assuming equal efficacy in terms of PFS between letrozole+lapatinib and trastuzumab+anastrozole.
- Utility values used for pre progression and post-progression (■■■■ and ■■■■) favoured lapatinib and letrozole, while the re-analysis by the EGP used more conservative values derived from the literature (0.81 and 0.58) *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)*

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

Although patient advocacy group input was not received for the lapatinib + letrozole review, input from other relevant pCODR reviews of breast cancer treatments was used to determine patient values and experiences with the disease. Patients had suggested that additional therapies that stop progression of the disease, even if only for a short amount of time, with manageable side effect profiles would be important to them. Patients also stated that they would be willing to tolerate the potential adverse effects of a treatment if it was found to prolong their survival, even for a short period of time.

Given the lack of head to head comparison between lapatinib+letrozole to trastuzumab+anastrozole and the limitations associated with the indirect comparison presented, the submitted analysis was unable to address these patient concerns.

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

The submitted model is overly complex in its design. The model relies on a macro to generate results for each alternative rather than a single sheet for each alternative. The model incorporates hundreds of named cells which make it difficult to verify all source material and all calculations within a reasonable time frame. Furthermore, it is unclear that the probabilistic sensitivity analysis is valid given the lack of individual sheets for each comparator.

The manufacturer submitted a partitioned-survival model, where survival and progression are modelled independently and it is assumed that a patient's risk of dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state. As a result, the submitted analysis resulted in a sizeable percentage of the total survival gain in post-progression state. Also, this approach is generally most appropriate when the survival distributions for OS are more or less complete. In cases where OS data is not mature, projections of OS beyond the end of follow-up may be associated with a higher degree of uncertainty than other modelling approaches. Therefore, a significant proportion of life expectancy gain is derived from extrapolated data not actual data, which results in a lot of uncertainty around the results. After considering other possible interpretations, the Economic Guidance Panel did not consider

it necessary to add any additional comments or clarifications into the economic guidance report with regards to the uncertainty in the post progression OS gain.

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 incorporation of trastuzumab plus anastrozole and anastrozole alone as comparators is based on an indirect comparison between these treatments and letrozole only for HER2+ positive patients. This is achieved by obtaining a HR for anastrozole versus letrozole through RCTs comparing both treatments to tamoxifen. As none of these studies assessed results specifically for the HER2+ population, the results of the indirect comparison should be interpreted with caution. This is in alignment with the published study which concludes “*results are based on indirect comparisons and a network analysis for which the basic assumptions of homogeneity, similarity and consistency were not fulfilled*” (emphasis added by pCODR) (Reimsma 2012). As a result a more conservative interpretation of the analysis may be to assume equal efficacy between lapatinib+letrozole and trastuzumab+anastrozole.

Utility values chosen favoured lapatinib versus letrozole and included an error in the model (decrement of ■■■ vs ■■■ in the post progression state) however this error was corrected for in the re-analysis. *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)*

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 HR for PFS for lapatinib+letrozole used in the model was ■■■. The submitted evaluation states that clinical effectiveness for lapatinib+letrozole versus letrozole only comes from the EGF30008 trial. However, the RCT reports a HR of 0.71; this HR is used in the revised analysis by EGP. *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)*

The imputed HR for PFS for lapatinib+letrozole versus trastuzumab+anastrozole is ■■■. *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)*. This is based on a network meta analysis (NMA) in which the authors clearly state that the results must be treated carefully because assumptions of homogeneity, similarity and consistency were not fulfilled. A more conservative estimate would be to assume equal PFS and OS for these comparators. Thus, the limitation of the NMA and the insignificance of the findings suggest that assuming that letrozole+lapatinib has superior overall and progression free survival than trastuzumab+anastrozole is inappropriate. After considering other possible interpretations, the Economic Guidance Panel did not consider it necessary to add any additional comments or clarifications into the economic guidance report with regards to the EGP’s more conservative approach of assuming equal PFS and OS for letrozole+lapatinib and trastuzumab+anastrozole.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

Proportion of patients currently treated with trastuzumab plus anastrozole who will move to lapatinib plus letrozole.

Whether patients receiving letrozole or anastrozole alone will move to lapatinib plus letrozole. It is not clear that this is a clinically realistic occurrence.

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

The analysis is well done in terms of technical quality. The major limitation as in all BIAs is the lack of data to support the assumptions made. Three specific assumptions need consideration.

- capture rate
- which drugs will be replaced.
- Jurisdiction's current effective prices

1.5 Future Research

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

The submitted model is not a true Markov model but rather a partitioned survival model, which leads to higher projections for the overall survival gain from lapatinib+letrozole. Re-analysis was conducted by the EGP to address this and it is recommended that any re-submission also incorporate a proper Markov model, to test the effect of the method used for extrapolating benefit gains.

Although the submitted model is a simple three state model incorporating side effects, it is excessively complex. Calculations are difficult to follow and there is a great degree of transparency lacking. The model would be greatly improved by providing a worksheet for each comparator rather than the current approach of using macros and relying on the use of the INDIRECT function.

The model results are highly reliant on an indirect comparison which uses data from trial populations that are not exclusively post menopausal women with hormone receptor positive and HER-2 positive metastatic breast cancer. This is stated in the associated publication “Indirect comparison results are based on a network analysis for which the basic assumptions of homogeneity, similarity and consistency were not fulfilled” (Riemsma 2012). Specifically, analysis included trials that did not exclusively assess for HER2+ patients. Given this, caution should be used in linking trastuzumab+anastrozole to lapatinib+letrozole, while the most conservative assumption may be to assume equal efficacy between these alternatives.

Is there economic research that could be conducted in the future that would provide valuable information related to lapatinib (Tykerb)?

A revised economic model addressing the above concerns would be helpful.

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 lapatinib (Tykerb) with letrozole for metastatic breast cancer. A full assessment of the clinical evidence of lapatinib (Tykerb) with letrozole for metastatic 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.pcodr.ca).

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.pcodr.ca). 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.

REFERENCES

Fleeman N, Bagust A, Boland A et al. Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis. *Health Technol Assess.* 2011;15(42):1-93

Hastings V, Delea TE, Amonkar M et al. Indirect comparison of the cost-effectiveness of letrozole plus lapatinib (LET+LAP) versus anastrozole plus trastuzumab (ANA+TZ) as first-line treatment for postmenopausal women with HER2+ and HR+ metastatic breast cancer (MBC) from the U.K. National Health Service (NHS) perspective. *J Clin Oncol* 28:15s, 2010 (suppl; abstr 1035)

Johnston S, Pippin J Jr, Pivot X et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol.* 2009 Nov 20;27(33):5538-46

Riemsma R, Forbes CA, Amonkar MM et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). *Curr Med Res Opin.* 2012 Aug;28(8):1263-79.