PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Everolimus (Afinitor) for Advanced Breast Cancer

March 25, 2013

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FUNDING

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

INQUIRIES

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

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Novartis Canada Inc** compared everolimus in combination with exemestane to exemestane alone for patients with advanced breast cancer previously treated with an alternative regimen. Everolimus and exemestane are both administered orally.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The Clinical Guidance Panel considered other treatment options for this population such as chemotherapy (e.g. vinorelbine), tamoxifen, or fulvestrant would be appropriate. The Submitter did not include these comparisons in modifications to the main economic analysis.

Patients considered the following factors important in the review of everolimus, which are relevant to the economic analysis: overall survival and achieving stable disease, toxicity and quality of life, close monitoring and oral administration of everolimus.

- Patients indicated that stopping the progression of the disease and extending life expectancy are important aspects when consideration is given to treatment. Once a treatment option eventually stops working it is important to patients that there continues to be other options to manage stable disease. These factors have been considered through modelling of the overall survival and progression free survival.
- The patient input indicated that toxicity and quality of life are also a high priority and the toxicity is not insignificant for everolimus with side effects similar to chemotherapy. These factors have been considered in the submitted model.
- Due to the necessity for close monitoring there may still be a need for patients to meet with their oncologist on a more regular basis. The analysis takes a perspective of a public payer and therefore patients' burden due to increased monitoring has not been included in the submitted model.
- Patients felt that oral administration is one of the benefits of everolimus. Oral admiration could not be considered in the economic evaluation since the submitted analysis does not include intravenous comparators.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for everolimus, and which are relevant to the economic analysis: potential of increased cost due to dose increase, monitoring costs and oral administration. A full summary of Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

- PAG mentioned the need for dose adjustment of everolimus therapy in this patient population. Since all doses of everolimus are priced the same, dose decreases for patients will require a combination of two doses (e.g. 2.5mg + 5mg to make 7.5mg) and is likely to increase the cost. This factor has not been included in the submitted model, but it has been explored in the EGP one-way sensitivity analysis.
- PAG noted that since aromatase inhibitors rarely have dose adjustments, monitoring this patient population for toxicity may be a new issue presenting a challenge to implementation. Monitoring costs have not been included in the submitted model.
- PAG also noted that oral administration is one of the benefits of everolimus. Oral admiration could not be considered in the economic evaluation since the submitted analysis does not include intravenous comparator.
- PAG noted uncertainty in the duration of treatment, where therapy could continue until no longer clinically beneficial or until unacceptable toxicity is observed in

patients. PAG identified as a potential barrier to implementation as it leads to uncertainty in the budget impact. The included model does not explicitly include discontinuations due to toxicity.

At the list price, everolimus costs $186.00 per 2.5 mg, 5 mg, or 10 mg tablets. At the recommended dose of 10 mg per day, the average cost per day in a 28-day course of everolimus is $186.00 and the average cost per 28-day course is $5,208. Exemestane is available as 25 mg tablet at a cost of $3.90. At the recommended dose of 25 mg per day, the average cost per day in a 28-day course of exemestane is $3.90 and the average cost per 28-day course is $109.20.

1.2 Summary of Results

The EGP's conservative estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is $162,049 or higher when everolimus plus exemestane is compared with exemestane alone. It should be noted that the above estimates did not account for structural limitations identified in the submitted model; hence, the estimate is most likely an underestimation of the actual incremental cost-effectiveness ratio. This estimate is based on reanalyses conducted by the Economic Guidance Panel and using the model submitted by Novartis Pharmaceuticals Canada Inc.

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

- the extra cost (ΔC) of everolimus is $43,489 over 5 years. Costs included drug costs, costs associated with management of serious adverse events and pre-progression and post-progression background costs.
- the extra clinical effect (ΔQALY or ΔLY) of everolimus is 0.27 QALYs or 0.41 life years(21.4 weeks). Key clinical effects included progression-free survival and overall survival estimates from BOLERO-2 study. The biggest influence on both QALYs and life years was the estimate of survival following tumour progression.

The higher bound of the incremental cost-effectiveness ratio cannot be estimated due to the model's inherent structural limitations that preclude EGP from addressing in the reanalyses.

This estimate is based on the Economic Guidance Panel reanalyses that assumed the model's time horizon to be shorter than the proposed lifetime time horizon modelled by the manufacturer as well as using the quality of life data for pre-progressed state based on the BOLERO-2 study. Given the model's heavy reliance on extrapolation for clinical benefit, it was felt appropriate to consider more conservative options related to shorter time horizons. The assumption that the time horizon should be reduced was supported by the pCODR Clinical Guidance Panel, who estimated that the vast majority of these patients will die within 5 years of initiating the treatment.

A major source of uncertainty of the model is that the overall survival data is not mature at this time, and that it is uncertain whether there will be a statistically significant overall survival benefit or what the magnitude of that benefit will be. The

manufacturer's base case estimate modeled a gain in survival by [redacted] years over 10 years ([redacted] years gained in the pre-progressed state and [redacted] years gained in the post-progressed state). (*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).* Based on the submitted structure of the model, EGP is not unable to provide sensitivity analysis to examine how much the ICER may change if the overall survival benefit is different from that assumed by the manufacturer. Generally, if the overall survival benefit is smaller than assumed by the manufacturer, the true ICER will be higher.

The ICER estimate of $162,049 assumed that the time horizon of the model was reduced to 5 years, since there is only 17.7 months of data available from the BOLERO-2 study, versus the 10 years modelled by the manufacturer. The quality of life data for pre-progressed state was based on the BOLERO-2 study versus the published study by Lloyd[1]. The extra costs associated with everolimus were $43,489 and the extra QALYs associated with everolimus were 0.27, **with all the gain achieved in pre-progression state**.

- The estimates above represent the EGP's estimates despite the model's inherent structural limitations that preclude EGP from addressing in the reanalyses. Therefore the estimates may potentially be an underestimation of the actual incremental cost-effectiveness ratio.

The EGPs estimates differed from the submitted estimates. In the Economic Guidance Panel reanalyses, when the time horizon was shortened to address the heavy reliance on extrapolation in the submitted model, extra QALY gains for everolimus were lower and there was a decrease in the extra healthcare-associated costs for everolimus. This occurs because **a significant portion of life expectancy gain (94%)** is derived from extrapolated data not actual data in the model. Also, the EGP felt that quality of life data for pre-progression state obtained in the BOLERO-2 study could be used in the base-case scenario, as opposed to the utility value from the published study by Lloyd [1].

The estimates would have differed even more had the structural limitations identified in the submitted model been addressed. The manufacturer submitted a model where survival and progression are modelled independently and where 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. That resulted with 41% of the total estimated survival gain to be in post-progression state, which is a counterintuitive result. The EGP noted the limitation with the model structure but was not able to address it through re-analysis.

According to the economic analysis that was submitted by Novartis Canada Inc, when everolimus plus exemestane is compared with exemestane:

- the extra cost of everolimus plus exemestane (ΔC) is $51,126 over a 10 year horizon. Costs considered in the analysis included drug costs, costs associated with treatment of adverse events and pre and post-progression background treatment costs.
- the extra clinical effect of everolimus plus exemestane (ΔE) is 0.47 quality-adjusted life years or [redacted] life years gained. (*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

clinical effect considered in the analysis was based on extrapolated overall survival and progression free survival data.

The submitter estimated that the incremental cost-effectiveness ratio (ΔC/ΔE) is $108,624 per QALY or $[redacted] per life year. (*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).* **It should be noted that using 10 years' time horizon results with 41% of the total survival gain achieved in post-progression state, due to the submitted model structure.**

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 Economic Guidance Panel upper estimate is based on a reanalysis which assumed that the time horizon of the model was reduced to 5 years, to align with the short term data for progression free survival and overall survival, as well as in line with the CGP anticipated that the vast majority will die within 5 years of initiating the treatment. The manufacturer forecasts PFS and overall survival using 17.7 months of clinical data. Also, the EGP's upper estimate uses the quality of life data for pre-progressed state based on the BOLERO-2 study versus the published study by Lloyd[1].

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

Yes. Based on patient advocacy group input, patients considered the following factors important in the review of everolimus and which were relevant to the economic analysis: overall survival and progression free survival, toxicity and quality of life, close monitoring and oral administration of everolimus. With the exception of implications due to close monitoring, these factors were addressed in the economic analysis when possible and appropriate.

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

No. 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 high percentage of the total survival gain (41%) in post-progression state, which is counterintuitive. 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, as in the BOLERO-2 study, projections of OS beyond the end of follow-up will be associated with a high degree of uncertainty. Therefore, a significant proportion of life expectancy gain (94%) in the 10-year model is derived from extrapolated data not actual data, which results in lot of uncertainty around the results.

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

A major assumption made in the manufacturer's model is that there is overall survival benefit. The model's base case assumed a gained in survival by [redacted] years. ([redacted] years gained in the pre-progressed state and [redacted] years gained in the post-progressed state). (*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).* At the moment, overall survival data for BOLERO-2 is not mature yet. Generally, if the overall survival benefit is smaller than assumed in the model, then the ICER will be higher.

In the submitted economic model, because survival and progression are modelled independently, there is no direct assessment of patient's risk of dying before tumour progression and patient's risk of dying after tumour progression. The length of the available data from the BOLERO-2 study is short (17.7 months) in comparison with the 10 year time horizon of the model. Therefore, the assumptions around extrapolation using short term data could have a pronounced effect on clinical effect estimates. Quality of life data was based on the published study.

Overall, the Economic Guidance Panel conducted some reanalyses to address some of these limitations, which led to higher estimates of the ICER. However, the limitation due to the chosen model structure cannot be addressed by the EGP.

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 cost data used seemed adequate and the EGP would have used similar data. However, estimates of the long term survival gains with treatment were uncertain due to an assumption relating to improved survival post progression. EGP would have used individual level data to estimate transition probabilities among the three markov states and would have conducted a Markov model instead of survival partitioned model, which might have accounted for differences in risk of death before and after tumour progression.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The manufacturer submitted a budget impact analysis that was not specific to any Canadian public drug plan which estimates of the increased costs for the three years subsequent to the listing of everolimus for advanced breast cancer. The budget impact analysis provided estimates of the increased costs for the three years subsequent to the listing of everolimus for advanced breast cancer in Canada for first, second and third line therapy. The key variables included in the manufacturer's budget impact analysis are: prevalence of post-menopausal metastatic breast cancer patients, estrogen receptor positive (ER+) patients, patients on hormonal treatment, patients on aromatase inhibitors treatment, treatment cost, treatment duration, proportion of population covered by a provincial public drug plan, and the market share for those who are covered for 1st, 2nd

and 3rd line therapy. The manufacturer's submitted extensive one-way sensitivity analyses varying many of the input variables and reported that treatment duration in second line has the most pronounced impact of the estimate. The results are also sensitive to disease prevalence, % of population covered by public drug plans and market shares.

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

The model structure of the budget impact analysis was appropriate. The key limitations of the submitted budget impact analysis relate to the limited data to support the assumptions relating to the market share of everolimus, as well as and uncertainty around the treatment duration. The magnitude of the impact of a dose adjustment of everolimus to the total budget cost was not assessed in the submitted analysis.

1.5 Future Research

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

An economic model which provides the opportunity to adjust the movement of patients from pre-progression to post-progression to death would have enabled more accurate estimation of cost-effectiveness estimates.

Is there economic research that could be conducted in the future that would provide valuable information related to everolimus for treatment of advanced breast cancer?

At this time, only interim results for PFS are available. The OS results, a reliable and preferred health outcome in cancer research, were immature. Assessment of the cost-effectiveness of everolimus once that data is mature and available would give more accurate estimates of cost-effectiveness and would reduce the uncertainty around it.

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 everolimus (Afinitor) for ABC. A full assessment of the clinical evidence of everolimus (Afinitor) for ABC 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:

1. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006 Sep 18 [cited 2009 Jul 8];95(6):683-90. Available from: http://www.nature.com/bjc/journal/v95/n6/pdf/6603326a.pdf

2. Piccart-Gebhart M, Noguchi S, Pritchard KI, Burris HA, Rugo HS. Everolimus for postmenopausal women with advanced breast cancer: Updated results of the BOLERO-2 phase III trial [abstract]. J Clin Oncol [Internet]. 2012 Jun [cited 2012 Sep 20];30(15_suppl (May 20 Supplement), 2012):599. Available from: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/559?sid=b35a3f90-7363-4f61-9b99-c1479f9b8c2c (Presented at Presented at American Society of Clinical Oncology Annual Meeting; 2012 Jun 1-5. Chicago).

3. Baselga J, Campone M, Piccart M, Burris HA, III, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med [Internet]. 2012 Feb 9 [cited 2012 Sep 20];366(6):520-9. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1109653

4. National Institute for Health and Clinical Excellence (NICE). Fulvestrant 500 mg for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer [Internet]. London (UK): NICE; 201. [cited 2012 Nov 16]. Available from: http://www.nice.org.uk/nicemedia/live/12967/55985/55985.pdf

5. Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, et al. Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study. J Clin Oncol. 2012 Aug 1;30(22):2718-24.

6. Committee for Medicinal Products for Human Use (CHMP). Afinitor: CHMP variation assessment report [Internet]. London: European Medicines Agency (EMA); 2012 Jun 21. [cited 2012 Sep 20]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001038/WC500130788.pdf