PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Sorafenib (Nexavar) for Differentiated Thyroid Cancer

July 16, 2015

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INQUIRIES

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

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Bayer** compared sorafenib to best supportive care for patients with locally advanced or metastatic differentiated thyroid cancer who are refractory to radioactive-iodine and are not candidates for surgery or radiotherapy with curative intent. Sorafenib is administered orally.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, as there is no standard of care for this group of patients.

Patients considered the following factors important in the review of sorafenib, which are relevant to the economic analysis: limited treatment options, absence of effective treatment options, extending the time that their cancer is progression-free and extending overall survival. In addition to these factors, patients noted that their quality of life while taking sorafenib was good, despite some of the negative side effects. The economic model considered all these factors in its analysis.

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

- Unmet need for patients, along with no current standard of care;
- Dosing of sorafenib, orally twice daily, is an enabler with no wastage and easily managed dose adjustments;
- Small incremental budget impact due to the small number of patients eligible.

Sorafenib costs $46.47 per 200 mg tablet. At the recommended dose of 800 mg daily, the daily cost of sorafenib is $186 daily or $5,208 per 28 days.

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $189,647 and $206,945 when sorafenib is compared with best supportive care.

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 of sorafenib is between $79,609 and $80,148 (ΔC). The factors that most influence cost are the dose intensity (which is used to calculate the drug cost per cycle), treatment duration, the extrapolation curve for progression-free survival and drug acquisition costs.
- the extra clinical effect of sorafenib is between 0.38 and 0.42 (ΔE). The factors that most influence clinical effects are the methods used to adjust for cross-over for overall survival, the intercept of the curve for overall survival and the time horizon.

The EGP based these estimates on the model submitted by Bayer and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- The time horizon was reduced to 7 years (from 10 years) based on feedback from the CGP and the point at which only 10% of patients remain alive, the extra cost of sorafenib is $73,216 ($\Delta C_1$) and the extra effectiveness is 0.42 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $174,195 (from $142,843).
- Treatment duration is set to 18 cycles (from 16.1 cycles calculated using the extrapolated progression-free survival curves), the extra cost of sorafenib is $81,371 ($\Delta C_2$) and the extra effectiveness is 0.52 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $155,961 (from $142,843).
- The upper 95% confidence interval of the intercept for overall survival is examined, the extra cost of sorafenib is $75,297 ($\Delta C_3$) and the extra effectiveness is 0.59 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $128,960 (from $142,843).
- The lower 95% confidence interval of the intercept for overall survival is examined, the extra cost of sorafenib is $73,443 ($\Delta C_4$) and the extra effectiveness is 0.43 (ΔE_4), which increases the estimated incremental cost-effectiveness ratio to $206,945 (from $142,843).

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Bayer, when sorafenib is compared with best supportive care:

- the extra cost of sorafenib is $74,527 ($\Delta C$). Costs considered in the analysis included drug costs, administration costs, routine care costs, adverse event costs, and end of life care costs. Note that wastage was not considered.
- the extra clinical effect of sorafenib is 0.52 quality-adjusted life years and 0.86 life years gained (ΔE). The clinical effect considered in the analysis was based on overall survival, progression-free survival, adverse events, treatment duration, and dose intensity. Note that subsequent treatment options were not considered.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $142,843.

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 changes in the estimates from the EGP include a shortened time horizon, a longer treatment duration to reflect treating beyond progression, and examining the 95% confidence intervals around the intercept for overall survival in order to account for some of the uncertainty in the extrapolation of the data. These factors, when considered together, increased the ICER.

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

Yes, factors important to patients—notably both progression-free and overall survival– are adequately addressed in the economic analysis. Quality of life is also addressed.

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

Yes – the design and structure of the submitted economic model is adequate. Many important clinical and cost inputs were considered. Both subsequent treatments and wastage were not considered in the analysis, however, the omission of these two inputs is unlikely to have a significant impact on the ICER.

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 submitter assumed that the patients in the clinical trial were similar to those in Canada; this is a reasonable assumption and given the small number of patients eligible, it would not have been possible to conduct the trial in Canada. The submitter also assumed that despite the fact that 60% of patients in the sorafenib arm were still undergoing survival follow-up, that overall survival data used would be the same for all patients. This assumption has an impact on the generalizability of the results and introduces a large amount of uncertaintly. The submitter also assumed that patients would not receive any subsequent treatments; costs with subsequent therapies may differ between treatment arms and could potentially affect the results. The submitter assumed that treatment duration was based on progression-free survival, however, the CGP stated that treatment duration may be longer than "treating until progression" and could significantly impact the costs.

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 submitter adjusted for cross-over in the analysis of overall survival due to the design of the randomized controlled trial. This decision to adjust did impact the results, though the EGP examined the difference in modifications to the main analysis. Further, because overall survival data was immature at the time of analysis, extrapolation was based on incomplete data. This introduced uncertainty into the results. Finally, though quality of life was collected in the trial, not all patients completed the questionnaire at follow-up. This completion rate differed between the two treatment groups, possibly introducing a bias (for example, those who completed were doing better than those who didn't, thus had a better quality of life).

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The cost drivers of the budget impact analysis are the number of patients treated, the cost of the drug and the market share of the drug. Given that there is no other suitable treatment for these patients, market share could potentially be high.

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

Given the small number of patients affected with RAI-R DTC, estimates for the number of patients were taken from the literature. There is no data on the number of eligible patients in Canada.

1.5 Future Research

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

Data source for treatment duration could come from multiple sources, to increase the generalizability beyond clinical trial data. For example, using both clinical trial data and expert opinion from oncologists in order to build in a range of possible treatment durations. This is even more important when treatment duration is a cost driver.

Is there economic research that could be conducted in the future that would provide valuable information related to sorafenib?

A randomized controlled trial where analysis was not dependant on adjustment for cross-over, with mature overall survival data, would allow for an examination of unadjusted overall survival hazard ratios.

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 Endocrine 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 Sorafenib (Nexavar) for Differentiated Thyroid Cancer. A full assessment of the clinical evidence of Sorafenib (Nexavar) for Differentiated Thyroid 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*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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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