pan-Canadian Oncology Drug Review Final Economic Guidance Report

Bevacizumab (Avastin) and Capecitabine for Metastatic Colorectal Cancer

July 21, 2015

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis submitted to **pCODR by Cancer Care Ontario's Gastrointestinal Disease Site Group** compared bevacizumab + capecitabine to capecitabine alone for first-line treatment of metastatic colorectal cancer (mCRC) in patients with mCRC who are not suitable for combination chemotherapy with irinotecan or oxaliplatin.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate.

Patients considered the following factors important in the review of bevacizumab + capecitabine, which are relevant to the economic analysis, and the key expectations of using bevacizumab are: more treatment options, prolonging survival and improving quality of life.

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

Clinical factors:
- The addition of bevacizumab to capecitabine may have additional benefits for a subgroup of patients
- Use beyond progression

Economic factors:
- Small subgroup of patients
- High cost of bevacizumab

At the disclosable price, bevacizumab costs $600.00 per 100mg vial and $2,400.00 per 400mg vial. At the recommended dose of 7.5 mg/kg on day 1 of every 3 weeks and assuming a 70 kg weight, bevacizumab cost $150.00 per day and $4,200.00 per 28-day course. At the submitted confidential price bevacizumab costs $⬛⬛⬛ per 100mg vial and $⬛⬛⬛ per 400mg vial. *(The cost of bevacizumab 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.)*

Capecitabine cost $1.525 per 500mg tablet. Based on a 1.75m^2 average body surface and at the recommended dose of 1000 mg/m^2 twice daily on days 1-14 of every 3 weeks, capecitabine cost $6.97 per day and $195.20 per 28-day course.

1.2 Summary of Results

The EGP's best estimates of the incremental cost-effective ratio ($\Delta C / \Delta E$), based on the submitted confidential price, ranged from $212,938/QALY to $309,763/QALY and $165,557/LY to $276,475/LY when varying some important assumptions on the type of model, OS extrapolations and utility values.

- The extra cost of bevacizumab + capecitabine is between $53,036 and $54,007. The factor that most influence the costs is the cost of bevacizumab.
- The extra clinical effect of bevacizumab + capecitabine is between 0.171 to 0.254 QALYs and 0.192 to 0.326 LYs. The factors that most influence the effectiveness of bevacizumab + capecitabine are the model type (Markov model or partitioned survival) and OS extrapolations.

The EGP based these estimates on the model (Markov and Partitioned survival curves models) submitted by the Cancer Care Ontario's Gastrointestinal Disease Site Group and reanalyses conducted by the Panel showed that when:

1. A Markov model and a 5-year time horizon are considered, the incremental cost of bevacizumab + capecitabine is $54,007 ($\Delta C_1$), and the incremental benefit of bevacizumab + capecitabine is 0.254 QALY (ΔE_1). These assumptions led to an estimated incremental cost-effectiveness ratio of $212,938/QALY gained. (*EGP's best estimate, lower limit*).

2. Partitioned survival curves model is considered as opposed to the Markov model, results are more conservative based on lower QALY gained (0.186 versus 0.254 QALYs gained). In the partitioned survival curves model results, the incremental cost of bevacizumab + capecitabine is $53,209 ($\Delta C_2$), and the incremental benefit of bevacizumab + capecitabine is 0.186 QALY (ΔE_2), based on a mean of 2.6 months gain in OS. In the AVEX study, the incremental OS gain was 3.9 months but was not shown to be statistically significant. However, in the model, mean PFS gain was estimated to 4.1 months with the combination which is similar to the median PFS gain (median=4 months) with bevacizumab + capecitabine in the AVEX study. These changes increased the estimated incremental cost-effectiveness ratio to $286,121/QALY gained.

3. Looking at the partitioned survival curves model, OS curves converge (no difference in OS benefit) at 40 months in the submitter's base case. However, in the AVEX study, OS curves converge at 27.5 months. In that case (OS converging at 27.5 months), the incremental cost of bevacizumab + capecitabine is $53,036 ($\Delta C_3$), and the incremental benefit of bevacizumab + capecitabine is 0.171 QALY (ΔE_3) (mean of 2.3 months gain in OS and 4.1 months gain in PFS). These changes increased the estimated incremental cost-effectiveness ratio to $309,763/QALY gained.

4. Utility values were reduced by 10%, in order to better quantify uncertainty related to the data source (utilities from 3 different sources in the base case and were not collected in the AVEX trial), the incremental cost of bevacizumab + capecitabine is $54,007 ($\Delta C_4$), and the incremental benefit of bevacizumab + capecitabine is 0.227 QALY (ΔE_4). These changes increased the estimated incremental cost-effectiveness ratio to $237,525/QALY gained.

5. The time horizon was reduced from 5 to 3 years, based on input from the CGP who advised that the time horizon in this treatment setting could vary between 3 and 5 years, the incremental cost of bevacizumab + capecitabine is $53,676 ($\Delta C_5$), and the incremental benefit of bevacizumab + capecitabine is 0.232 QALY (ΔE_5). These changes increased the estimated incremental cost-effectiveness ratio to $230,978/QALY gained.

6. When the above four parameters, partitioned model (with OS curves that converge at 27.5 months), time horizon (reduced to 3 years) and utility values (reduced by 10%), are varied simultaneously, the incremental cost of bevacizumab is $52,924 ($\Delta C_6$), and the incremental benefit of bevacizumab+capecitabine is 0.153 QALY (ΔE_6). These changes increased the estimated incremental cost-effectiveness ratio to $346,078/QALY gained (*EGP's best estimate, higher limit*).

In a sensitivity analysis, the MAX study results were also considered (PFS HR=0.63) in order to quantify uncertainty related to the AVEX study results. Particularly, this sensitivity analysis was conducted to take into account the uncertainty related to the external validity of the AVEX study with regards to age (patients in MAX study were slightly younger. Based on the PFS HR observed in the MAX study, the incremental cost of bevacizumab + capecitabine is $49,703 ($\Delta C_7$), and the incremental benefit of bevacizumab+capecitabine is 0.171 QALY (ΔE_7). These changes increased the estimated incremental cost-effectiveness ratio to $290,663/QALY gained.

Moreover, results are sensitive to treatment duration. In the base case, based on PFS, the median treatment duration in the model were approximately 5.5 months in the capecitabine group and 9.5 months in the bevacizumab + capecitabine group. Corresponding median treatment durations

in the AVEX study were lower (4.2 months and 5.8 months). The higher the treatment duration estimations, the higher the cost of treatment. However, the model did not account for dose adjustments, although a large proportion of patients had dose adjustments in the AVEX study. The effect of treatment duration on the ICUR have not been quantified and represent a source of uncertainty. Finally, the EGP considered that vial sharing could slightly decrease the incremental cost-effectiveness ratio. In the EGP's best estimates, treatment duration, vial sharing variations, 5-FU use, and age were not quantified but were also considered as a source of uncertainty.

The EGPs estimates differed from the submitted estimates.

According to the base case scenario of the economic analysis that was submitted by the Cancer Care Ontario's Gastrointestinal Disease Site Group, when bevacizumab + capecitabine is compared to chemotherapy alone:

- the extra cost of bevacizumab + capecitabine is $54,007 ($\Delta C$). Costs considered in the analysis included drug cost, administration costs, supplies, clinic visit costs, hospitalization costs, adverse event costs and best supportive care costs.

- the extra clinical effect of bevacizumab + capecitabine is 0.326 life years (LY) gained or 0.254 quality-adjusted life years (QALY) gained (ΔE). The clinical effect considered in the analysis was based on overall survival and progression-free survival.

The submitter estimated that the incremental cost-effectiveness ratio ($\Delta C/\Delta E$) was $165,557 per LY gained or $212,938 per QALY gained.

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?

There is uncertainty regarding the benefits in OS beyond the trial period as they were extrapolated in the model, particularly the magnitude of difference in OS is uncertain. While the reference case provided by the submitter used a simulated mean difference in OS that is higher than the trial median difference (not statistically significant), the exploration of uncertainty by the submitter was adequate. The submitter has submitted a series of scenarios analyses and one-way sensitivity analyses to explore the inherent uncertainty in incremental survival between the two treatment arms. Some of these scenarios were considered as possible by the EGP. The results are most sensitive to the type of economic model (Markov model or partitioned survival curves model), utility values, OS extrapolations, and PFS hazard ratios.

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

Based on the pCODR patient advocacy group input, patients are seeking to have more treatment options, to prolong survival and to see an improvement in the quality of life. These factors have been captured in the submitter's cost-utility analysis.

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

The design and structure of the submitted economic model is adequate for summarizing the evidence and answering the relevant questions. However, the model does not allow the full exploration of uncertainty. Some important assumptions have to be modified to reflect the CGP and EGP's opinion.

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?

Most assumptions made in this economic model were based on the AVEX and MAX trial data and considered to be appropriate. The submitter also consulted clinical expert opinion in order to ensure the model's subsequent treatments reflect Canadian practices.

OS and PFS were the key clinical inputs for the economic submission and the estimation of the cost-effectiveness of bevacizumab + capecitabine. The incremental benefits of bevacizumab + capecitabine were generated from the AVEX trial data. OS extrapolation based on Markov model or partitioned survival curves model led to pharmacoeconomic uncertainty that has been well quantified. Furthermore, treatment duration has an impact on total costs and is crucial to the estimation of the cost-effectiveness of bevacizumab + capecitabine in this population. Utility values considered also represent an important assumption affecting results as they directly impact utility gain estimation. Time horizon of the model affects results as the lower this is, the higher the ICER. A shortened time horizon from 5 to 3 years was also considered as a plausible scenario by EGP and CGP. Wastage is also an important consideration when estimating the cost of the drug. Both scenarios, with or without wastage, were presented. The submitter conservatively considered possible wastage in the base case. Moreover, toxicities associated with bevacizumab and their costs are important variables that were captured in the model.

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 questions?

While the projected survival benefits in the reference case (Markov model) were possible assumptions, inherent uncertainty in the OS difference between the two groups should have been better quantified in the submitted model. Moreover, when the EGP's best assumptions were considered in the model, particularly those on partitioned survival curves and OS (curves equal after 27.5 versus 40 months), the incremental costs were higher and incremental benefits were lower than those estimated by the submitter in the base case. This led to higher incremental cost-utility ratios.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

A budget impact analysis (BIA) was submitted to determine the impact of bevacizumab (in combination with capecitabine) listing (over a three-year time horizon) to the Cancer Care Ontario New Drug Funding Program for the requested indication. Assumptions were made based on available epidemiological estimates, market share assumptions and published literature. Budget impact would be greater with a higher metastatic disease prevalence (higher number of eligible patients) and higher bevacizumab market shares. Actual percentage of patients treated, dose intensity and average BSA can also impact the estimations. Budget impact could also depend on wastages. Inappropriate use outside the indication, for example maintenance therapy after progression, might also potentially increase the budget impact.

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

Limitations of the budget impact analysis include the uncertainty surrounding the impact of the mentioned assumptions on the estimations.

1.5 Future Research

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

There was some but not enough flexibility in the submitted model to explore inherent uncertainty with regards to the mean treatment duration based on PFS. Moreover, better quantification of the uncertainty around some important parameters (5-FU use, potential bevacizumab use beyond progression, toxicities and time horizon), would have improved the evaluation.

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

The submitted model was generally well conducted and it allowed exploration of major uncertainties. Another pharmacoeconomic study conducted in a relevant setting was published based on the MAX study results (Carter 2014). The purpose of this study was to evaluate the cost-effectiveness of adding bevacizumab to capecitabine monotherapy in patients with metastatic colorectal cancer, using data from the prospective economic evaluation conducted alongside the MAX trial. Future research, by independent groups, in this patient population incorporating the use of 5-FU as well as capecitabine would provide valuable information.

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 Gastrointestinal 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 bevacizumab (Avastin) in combination with capecitabine. A full assessment of the clinical evidence of bevacizumab (Avastin) in combination with capecitabine for the first-line treatment of metastatic colorectal 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 of the economic model, 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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