PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Bevacizumab (Avastin) for Cervical Cancer

March 23, 2015

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

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

TABLE OF CONTENTS

DISCLAIMER & FUNDING i

INQUIRIES ii

TABLE OF CONTENTS iii

1. ECONOMIC GUIDANCE IN BRIEF 1

    1.1. Background 1

    1.2. Summary of Results 1

    1.3. Summary of Economic Guidance Panel Evaluation 3

    1.4. Summary of Budget Impact Analysis Assessment 4

    1.5. Future Research 4

2. DETAILED TECHNICAL REPORT 6

    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 7

REFERENCES 8

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Hoffmann-La Roche Limited** compared bevacizumab + chemotherapy to chemotherapy alone for patients with persistent, recurrent or stage IV carcinoma of the cervix.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. **Patients** considered the following factors important in the review of bevacizumab, which are relevant to the economic analysis, and the key expectations of using bevacizumab are: to prolong survival, tumour shrinkage, and to see an improvement in the 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, and which are relevant to the economic analysis: small patient population, add-on to existing therapy that has additional clinical benefits, the high cost of bevacizumab and the additional nursing, lab, physician and pharmacy resources required for safe preparation and administration of bevacizumab.

At the disclosable price bevacizumab costs $600.00 per 100mg vial and $2400.00 per 400mg vial. At the recommended dose of 15 mg/kg on day 1 for 21 days, bevacizumab cost $300.00 per day and $8400.00 per 28-day course. At the submitted confidential price bevacizumab costs $[redacted] per 100mg vial and $[redacted] 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.)*

Cisplatin cost $0.16 per 1 mg/mL. At the recommended dose of 50 mg/m^2, cisplatin cost $0.65 per day and $18.13 per 28-day course. Paclitaxel costs 0.3320/mg^2. At the recommended dose of 135 or 175 mg/m^2 on day 1, paclitaxel cost $3.63-4.70 per day and $101.59-131.69 per 28-day course. Topotecan cost $141.00/mg. At the recommended dose of 0.75 mg/m^2 on days 1 to 3, topotecan costs $25.68 per day and $719.10 per 28-day course.

1.2 Summary of Results

The EGP's best estimates of the incremental cost-effective ratio (ΔC/ΔE), based on the submitted confidential price, ranged from $157,829/QALY to $245,452/QALY and $117,067/LY to $168,497/LY when varying some important assumptions on OS extrapolations, utility values, time horizon and mean body weight.

- The extra cost of bevacizumab plus chemotherapy is between $43,872 and $47,107. The factors that most influence the costs are treatment duration and mean body weight.
- The extra clinical effect of bevacizumab plus chemotherapy is between 0.192 to 0.278 QALYs and 0.280 to 0.375 LYs. The factors that most influence the effectiveness of bevacizumab plus chemotherapy are OS extrapolation, time horizon and utility values.

The EGP based these estimates on the model submitted by Hoffmann-La Roche Ltd. and reanalyses conducted by the Panel showed that when:

1. The time horizon was reduced to 10 years, based on input from the Clinical Guidance Panel, the incremental cost of bevacizumab is $43,872, and the incremental benefit of bevacizumab is 0.278 QALY. These changes increased the estimated incremental cost-effectiveness ratio to $157,829/QALY gained (*EGP's best estimate, lower limit*).

2. OS curves converge (no difference in OS benefit) at 120 months, the incremental cost of bevacizumab is $42,955, and the incremental benefit of bevacizumab is 0.213 QALY based on a mean 3.4 months gain in OS, which is similar to the OS gain with bevacizumab in the GOG-240 study. These changes increased the estimated incremental cost-effectiveness ratio to $201,433/QALY gained.
3. Utility values were reduced by 10%, in order to better quantify uncertainty related to the non-trial data source, the incremental cost of bevacizumab is $44,228, and the incremental benefit of bevacizumab is 0.273 QALY. These changes increased the estimated incremental cost-effectiveness ratio to $162,175/QALY gained.
4. Mean body weight is increased by 10% (to 69.9kg), the incremental cost of bevacizumab is $48,380, and the incremental benefit of bevacizumab is 0.303 QALY. These changes increased the estimated incremental cost-effectiveness ratio to $159,657/QALY gained.
5. OS curves (converge at 120 months), time horizon (10 years), utility values (reduced by 10 %) and mean body weight (increased by 10 %) are varied simultaneously, the incremental cost of bevacizumab is $47,107, and the incremental benefit of bevacizumab is 0.192 QALY. These changes increased the estimated incremental cost-effectiveness ratio to $245,452/QALY gained (*EGP's best estimate, higher limit*).

Moreover, results are sensitive to treatment duration. When considering a higher treatment duration (8.2 months based on PFS as a proxy) as opposed to the median treatment duration observed in the clinical trial (7 cycles) the ICUR increases significantly. The mean treatment duration was slightly higher (7.5 cycles) than the median treatment duration, therefore the costs and the ICUR would consequently increase if the mean treatment duration were used. Finally, the EGP considered that vial sharing could decrease the incremental cost-effectiveness ratio. However, in the EGP's best estimates, treatment duration and vial sharing variations were not quantified but were considered as a source of uncertainty.

The manufacturer's base case assumed a mean difference in overall survival that is higher than the median difference in overall survival observed in the GOG-240 study (Tewari 2014). This estimate is uncertain because a high proportion of the mean overall survival benefit was estimated by extrapolation of survival curves. The EGP considered that the pCODR CGP accepted that there is a net overall clinical benefit of bevacizumab based on the results of the GOG-240 study, the true magnitude of this difference from available data is uncertain. As such, with the submitted reference case using survival curves from the trial and OS and PFS curves extrapolations, the ICUR is estimated by the manufacturer to $145,957 per QALY gained based on an OS gain of 4.9 months (ΔE 0.412 LY or 0.303 QALY and ΔC $44,228). If this survival benefit is less than that assumed in the manufacturer's base case, or survival benefit attenuates over time, the ICUR could be higher.

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Hoffmann-La Roche Limited, when bevacizumab plus chemotherapy is compared to chemotherapy alone:

- the extra cost of bevacizumab plus chemotherapy is $44,228 (ΔC). Costs considered in the analysis included drug cost, administration costs, health state costs, adverse event costs and end-of-life care costs.
- the extra clinical effect of bevacizumab plus chemotherapy is 0.412 life years (LY) gained or 0.303 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 (ΔC / ΔE) was $107,456 per LY gained or $145,957 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 and PFS 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 uses a simulated mean difference in OS that is higher than the trial median difference, the exploration of uncertainty by the submitter was sub-optimal. The manufacturer has submitted a series of one-way sensitivity analyses to explore the inherent uncertainty in incremental survival between the two treatment arms. The results are most sensitive to mean body weight, utility values, OS extrapolations, and time to off treatment. The EGP also considered a lower time horizon.

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 prolong survival, tumour shrinkage, and to see an improvement in the quality of life.

Quality of life, progression-free survival and life expectancy have been captured in the manufacturer's economic submission in their 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 pharmacoeconomic model were based on the GOG-240 trial data and considered to be appropriate or possible. The submitter also consulted clinical 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. The incremental benefits of bevacizumab were generated from the GOG-240 trial data. OS extrapolation led to pharmacoeconomic uncertainty that has to be quantified. Moreover, the model generated a post-progression survival gain representing 44% of the total OS gain. This substantial gain in OS was modelled to occur after patients had progressed and were no longer treated with bevacizumab. The clinical plausibility of such substantial OS gain in post-progression survival is uncertain. Furthermore, treatment duration has an impact on total costs and is crucial to the estimation of the cost-effectiveness of bevacizumab 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 also affects results as the lower this is, the higher the ICER. A shortened time horizon to 10 years was considered by EGP. 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 in the model. Finally, as the drug dosage depends on the weight of the patient, the average weight considered in the model is important when estimating the cost of the drug and consequently its cost-effectiveness.

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 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 OS, utility values, time horizon of the model, and average weight, the incremental costs were higher and incremental benefits were lower than those estimated by the submitter. This led to higher incremental cost-utility ratios. Toxicities costs (particularly febrile neutropenia and fistulas) could be higher than those estimated by the manufacturer. However, cost-effectiveness results were not sensitive to this parameter.

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 the introduction of bevacizumab (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 research and published literature. Budget impact would be greater with a longer duration of therapy, higher number of eligible patients, higher bevacizumab market share, and higher mean body weight. 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 a new entry for treating cervical cancer as currently there is no standard treatment other than chemotherapy. Limitations also include uncertainty surrounding the impact of the assumptions of market share, treatment duration, number of eligible patients, body weight, and wastages.

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 when modelling the survival curves during and beyond the trial period in one way sensitivity analysis or PSA. This is also the case for the mean treatment duration considered in the model. Moreover, better quantification of the uncertainty around utility values and toxicities, along with a shorter 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?

There are no other economic evaluations on bevacizumab in the indicated patient population. A complete validation through independent research would be valuable in this patient group.

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 Genitourinary 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). A full assessment of the clinical evidence of bevacizumab (Avastin) for advanced, recurrent or metastatic cervical 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

AVASTIN® (Bevacizumab) Budget Impact Analysis Report. Prepared for Hoffman-La Roche Ltd. 2014. (*confidential)*

Avastin (Bevacizumab) Cost Effectiveness Model - Avastin for the treatment of patients with persistent, recurrent or metastatic cervical cancer based on the GOG 0240 trial. Prepared for Hoffman-La Roche Ltd. 2014. (*confidential)*

Avastin Product Monograph. Available at: http://www.rochecanada.com/fmfiles/re7234008/Research/ClinicalTrialsForms/Products/ConsumerInformation/MonographsandPublicAdvisories/Avastin/Avastin_PM_E.pdf. Last update 27 June 2014. Accessed 29 August 2014.

Davy MLJ, Dodd TJ, Luke CG, and Roder DM. Cervical Cancer: Effect of Glandular Cell Type on Prognosis, Treatment, and Survival. Obstet Gynecol 101 (2003): 38-45.

Kitagawa R, Katsumata N, Ando M, et al. A multi-institutional phase II trial of paclitaxel and carboplatin in the treatment of advanced or recurrent cervical cancer. Gynecol Oncol. 2012 May;125(2):307-11

Naik H, Brown MC, Eng L, Pringle D, Mahier M, Hon H. Characterizing Health Utility values of Canadian Cancer Patients. Poster presented at ISPOR Conference (2014).

Teckle P, McTaggart-Cowan H, Hoek KVd, Chia S, Melosky B, Gelmon K, Peacock S. (2013). Mapping the FACT-G cancer-specific quality of life instrument to the EQ-5D and SF-6D. health and Quality of Life Outcomes, 11:203.

Tewari KS, Sill MW, Long HJ, et al. Improved survival with bevacizumab in advanced cervical cancer. New Engl J Med 2014;370(8):734-43.