PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Bevacizumab (Avastin) for Ovarian Cancer

June 4, 2015

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The economic analysis **submitted to pCODR by Hoffmann-La Roche Limited** presents a cost-utility analysis of carboplatin, bevacizumab (Avastin) plus paclitaxel (CBP) in comparison to carboplatin plus paclitaxel (CP) as a front-line treatment for patients with Stage III Suboptimal Debulking, Stage III Unresectable, or Stage IV epithelial ovarian cancer (OC), primary peritoneal cancer or fallopian tube cancer. The Submitter used a partition model based on progression-free survival and overall survival. All drugs in both treatment and control arms are administered intravenously. Bevacizumab is administered intravenously at a dose of 7.5mg/kg every three weeks. According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate since no other novel, effective treatments exist for this population and CP is the standard of care in many jurisdictions. The evidence of relative effectiveness for CBP originate from ICON7 a randomized clinical trial (RCT). In particular, given that the economic study focused on a subpopulation of the ICON 7 study, it used a post-hoc modification of a preplanned high risk for progression subgroup analysis (the *modified high risk for progression* subgroup) of ICON7. Although subgroup analyses suffer from imbalance between groups and inadequate sample size for hypothesis testing, the CGP felt that the study was adequately powered to detect a true survival effect, the results were in line with other RCTs of bevacizumab (e.g. the GOG-218 study) and the results were also biologically plausible. Modifications in the main analysis take into account the uncertainty around the survival benefit, the quality-of-life (QoL) estimates, the model's time horizon, administration costs, etc, were undertaken both from the submitter and the EGP.

Patients advocacy groups considered the following factors as important in the review of bevacizumab, which are relevant to the economic analysis: extending survival, improving QoL, effectively managing tumour growth, and reducing adverse events associated with some of the existing treatments (e.g. reducing ascites). The caregivers considered anxiety, stress and fatigue as being the most significant factors, followed by feelings of isolation, sleep issues, diet, physical strain and depression. The economic analysis did not incorporate any effect of the treatments on caregiver burden. Although the caregiver burden might be significant, the conventional methods followed in economic models do not consider any caregiver effects. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

A **Provincial Advisory Group** (PAG) identified the high cost of bevacizumab, the additional resource utilization due to the preparation, administration and monitoring of bevacizumab, and drug wastage as important factors that need to be considered in the economic analysis. All factors above were considered in the economic analysis.

At the disclosable price, bevacizumab costs $600.00 per 100mg vial and $2400.00 per 400 mg vial. At the recommended dose of 7.5 mg/kg every 21 days, and assuming a body weight of 70 kg, bevacizumab costs $150.00 per day and $4200.00 per 28-day course. At the submitted confidential price, bevacizumab costs $[redacted] per 100mg vial or $[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.)*

Carboplatin costs $0.1000 per mg. At the dosing regimen of 5 mg/mL/min AUC (900 mg/m^2 on average), every 21 days, carboplatin costs $7.2857 per day and $204.00 per 28-day course.

Paclitaxel costs $0.3320 per mg. At the dosing regimen of 135-175 mg/m^2 on day 1 every 21 days, and assuming a body surface area of 1.7 m^2, paclitaxel costs $3.63 to $4.70 per day and $101.59 to $131.69 per 28-day course.

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $87,033 and $113,473 per quality-adjusted life years (QALYs) when bevacizumab+carboplatin+paclitaxel is compared with carboplatin+paclitaxel.

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 CBP is between $35,158 and $36,943. The most influential components of costs are the time horizon, the cost of treatment and cost of administration
- the extra clinical effect of CBP is between 0.317 and 0.424 QALYs. The most influential components of effectiveness were the survival effect of CBP, the time horizon assumed and the utility values for both progression-free and progressed states. The EGP based these estimates on the model submitted by Hoffman-La Roche Limited and reanalyses conducted by the EGP.

The reanalysis conducted by the EGP using the submitted model showed that when:

- QoL estimates per treatment arm, originating from the high-risk subgroup of the ICON7 study were used, the QALYs gained were 0.330, which increased the estimated incremental cost-effectiveness ratio to $108,223.77/QALY .
- The effectiveness of CBP is collected from the originally pre-planned subgroup analysis, the QALYs gained were 0.424 and the incremental costs were $36,943, which decreased the incremental cost-effectiveness ratio $87,033/QALY.

The cost-effectiveness estimates from the EGP reanalyses were within the range of estimates submitted by Hoffmann-La Roche Limited.

According to the economic analysis that was submitted by Hoffmann-La Roche Limited, when CBP is compared with CP:

- the extra cost of CBP is $36,021(ΔC). Costs considered in the analysis included cost of treatment, administration costs, costs associated with adverse events and wastage costs.
- the extra clinical effect of CBP is 0.374 QALYs gained (ΔE). The clinical effect considered in the analysis was based on QoL differences associated with longer stay in the progression-free and the post-progression states, and with survival benefits associated with CBP.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $96,261/QALY

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?

Overall, little differences between the reanalysis of EGP and the original submission were identified. The key reasons for differences between the submission and the EGP were assumptions on the level of pre-and post-progression QoL.

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

The patient advocacy group indicated that patients are interested in the effect of CBP on extending survival, improving QoL, reducing patients' pain stress and anxiety, and reducing tumour recurrence. Patients also indicated that they are willing to tolerate adverse events for a more effective treatment. The model considered the impact of CBP on some of these aspects. The patient advocacy group also identified a significant physical and psychological burden on caregivers. The model was not designed to address any caregiver burden.

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

Yes, the design of the submitted economic model is adequate and no changes in the model are needed

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 a 10 year time horizon as the base case of the economic model. That required the extrapolation of the RCT data for 4 years into the future. Given a survival benefit associated with CBP, this extrapolation resulted in a larger treatment benefit. The assumption, however, was in line with the CGP's opinion. The clinical effect of CBP was assumed to be both on reducing the probability of death and progression. The subgroup analysis of the ICON7 study supported such assumptions, although this input needs to be interpreted in light of the limitations of an RCT subgroup analysis. Finally, in the ICON7 trial a larger relative effect of CBP on overall survival was observed, as compared to the CBP effect on progression-free survival. This in turn resulted in significant post-progression survival benefits for the CBP arm observed in the submitted economic study. This post-progression benefit was observed both when a lifetime horizon and a horizon equal to the RCT's maximum follow up time was assumed. The clinical and economic findings have to be interpreted in light of this post-progression survival benefit observed both within and beyond the ICON7 trial.

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?

Yes. This was a well-designed economic evaluation. The EGP had some concerns with respect to the robustness of the RCT evidence and the way adverse events and QoL were incorporated in the model. However, after reanalysis from the EGP the results of the economic evaluation were not drastically different.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The submitter provided a budget impact analysis that forecasts the absolute costs following market introduction of bevacizumab. The factors that strongly affect the budget impact analysis were: the cost of bevacizumab, the prevalence of ovarian cancer and the probability of suboptimal debulking, the proportion of patients covered by a public healthcare plan, and the proportion of those with stage III or stage IV ovarian cancer.

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

Key limitations in the budget impact analysis include: lack of province specific evidence regarding the epidemiological inputs, as well as the market share input. In addition, the budget impact analysis submitted does not take into account the fact that patients will survive longer with bevacizumab and therefore the use will be higher. Finally, indication creep was not adequately considered in the estimates of the BIA. Given that CBP is applied in a specific population (patients with Stage III Suboptimal Debulking, Stage III Unresectable, or Stage IV epithelial ovarian cancer (OC), primary peritoneal cancer or fallopian tube cancer), the BIA may underestimate the true budget impact if significant indication creep occurs.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved? Is there economic research that could be conducted in the future that would provide valuable information related to CBP for ovarian cancer?

More information on the relative effectiveness of the CBP treatment on the high risk populations with respect to overall survival, QoL and adverse effects. Although not necessary for this review process, incorporating the caregiver burden within the decision model could help answer the patient advocacy group concerns.

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 Gynecological 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) for Ovarian Cancer. A full assessment of the clinical evidence of Bevacizumab (Avastin) for Ovarian 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, 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 Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

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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