



pan-Canadian Oncology Drug Review Final Economic Guidance Report

Bevacizumab (Avastin) for Platinum Resistant Ovarian Cancer

May 5, 2016

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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.

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Hoffmann-La Roche compared bevacizumab in combination with chemotherapy (paclitaxel, topotecan, or pegylated liposomal doxorubicin) to chemotherapy alone (paclitaxel, topotecan, or PLD) for patients with platinum-resistant ovarian cancer (PROC).

Table 1. Summary of submitted economic model

Funding Request	<i>Bevacizumab in combination with chemotherapy for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than two prior chemotherapy regimens (defined as number of lines of therapy/treatment since diagnosis with ovarian cancer)</i>
Type of Analysis	CUA
Type of Model	<i>Partitioned-survival model (area under the curve)</i>
Comparator	<i>Chemotherapy as defined as paclitaxel, topotecan or pegylated liposomal doxorubicin</i>
Time Horizon	6-8 years
Year of costs	2014 (where stated)
Perspective	Government payer
Cost of bevacizumab (used in the model)	<ul style="list-style-type: none"> • 15 mg/kg every 21 days • \$████ per 100 mg vial / \$████ per 400 mg vial* • \$████ per three week cycle without vial sharing per actual dose* (<i>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.</i>)
Cost of paclitaxel (used in the model)	<ul style="list-style-type: none"> • 175 mg/m² every 21 days • \$8.25 per 25 mL vial / \$16.50 per 50 mL vial • \$156.75 per three week cycle of paclitaxel without vial sharing per actual dose
Cost of topotecan (used in the model)	<ul style="list-style-type: none"> • 1.5 mg/m² for 5 consecutive days every 21 days • \$28.20 per 1 mL vial / \$112.80 per 4 mL vial • \$2,397.00 per three week cycle of topotecan without vial sharing per actual dose
Cost of pegylated liposomal doxorubicin (used in the model)	<ul style="list-style-type: none"> • 40 mg/m² every 21 days

	<ul style="list-style-type: none"> • \$341.50 per 10 mg vial / \$1,707.50 per 50 mg vial • \$2,390.50 per three week cycle of PLD without vial sharing per actual dose
Cost of gemcitabine	<ul style="list-style-type: none"> • 1000 mg/m² twice every 21 days • \$0.06 / mg • \$210.55 per three week cycle of gemcitabine without vial sharing per actual dose
Model Structure	A partitioned survival model is where overall survival is separated into progression-free survival (PFS) and post-progression survival (PPS) (total of three health states, with death as the third state). Patients enter the model in a progression-free survival health state having received platinum-based therapy.
Key Data Sources	<i>AURELIA trial data</i> ¹
Notes: *Disclosable price of bevacizumab is \$600 per 100 mg vial and \$2,400 per 400 mg vial. The cost per three-week cycle, without vial sharing and assuming the recommended dose, is \$6,600.	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of bevacizumab plus chemotherapy (topotecan, paclitaxel, or pegylated liposomal doxorubicin) with chemotherapy alone (topotecan, paclitaxel, or pegylated liposomal doxorubicin) is appropriate, given the lack of one standard of care for those on chemotherapy. Though a comparison was provided comparing bevacizumab plus weekly paclitaxel to paclitaxel alone, this sub-group analysis was unplanned and may not be powered to detect a difference between groups. Therefore, this sub-group analysis has been disregarded.

- Relevant issues identified by the CGP included:
 - *Net clinical benefit with bevacizumab is uncertain for overall survival as it was a secondary outcome and was confounded by cross-over to bevacizumab monotherapy from the chemotherapy alone arm after progression*
 - *There is net clinical benefit based on the statistically significant but clinically modest improvement in progression-free survival*
 - *Serious adverse events such as fistula, GI perforations, and thrombosis were more commonly observed with the use of bevacizumab, but were still rare (<4%) and manageable*
 - *Given the careful patient selection of the trial population, the results of the trial and economic model may not be generalizable to all patients with PROC*

Summary of patient input relevant to the economic analysis

Patients considered prolonged overall survival, prolonged progression-free survival and an improvement in quality of life as important factors for new treatments of PROC. Patients also identified adverse events as being an important consideration in the treatment they receive. All these factors were incorporated into the economic model.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
 PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for bevacizumab in combination with chemotherapy which are relevant to the economic analysis.

Enablers:

- Bevacizumab may have additional benefits for certain subgroups of patients. The potential effectiveness of bevacizumab has been used in the economic model.

Barriers:

- High cost of bevacizumab. The cost of bevacizumab, along with scenario analyses of 20% increase in cost, have been considered in the economic analysis.
- Unknown duration of treatment. Treatment duration in the economic model was based on the actual treatment duration from the AURELIA trial. The CGP indicated that this represented the most likely real-world scenario.
- Resources required to monitor and treat adverse effects. The incidence of adverse events and the resources required to treat them have been considered in the economic model.
- Additional infusion day to accommodate bevacizumab for patients receiving pegylated liposomal doxorubicin.
- Vial wastage. The base case analysis of the submitter assumed no vial sharing, a conservative estimate.

1.3 Submitted and EGP Reanalysis Estimates

Estimates	Submitted	EGP Reanalysis
ICER estimate (\$/QALY), range/point	\$240,100 - \$300,296	\$289,467 - \$425,651
ΔE (QALY), range/point	0.167 - 0.212	0.116 - 0.173
ΔE (LY), range/point	0.231 - 0.312	0.140 - 0.244
ΔC (\$), range/point	\$50,038 - \$50,812	\$49,247 - \$50,812

The main assumptions and/or limitations with the submitted economic evaluation were:

- A study design allowing cross-over. The submitter provided both an adjusted and unadjusted analysis to account for this limitation in study design.
- PFS was used as the primary end-point in the clinical trial AURELIA. The use of PFS as a primary end-point was assumed to be a valid surrogate outcome for OS end-point.
- The effectiveness across the various chemotherapy regimens is equivalent in the economic model (assumption).
- Uncertainty in the overall survival estimates (limitation).

1.4 Submitted and EGP Reanalysis Estimates

EGP Reanalysis

The EGP made the following changes to the economic model, using as a baseline the Submitter’s estimates that were adjusted for crossover:

- Overall survival is based on the lower 95% confidence interval of the Kaplan-Meier curve, with a parametric gamma tail, instead of the gamma parametric curve. The CGP indicated that there was uncertainty around overall survival. Using the lower 95% CI for overall survival allows the EGP to incorporate uncertainty into the best estimate. In addition, using the KM data ensures that the overall survival accrued in the model is equivalent to that accrued during the clinical trial and only uses the parametric function to extrapolate

the overall survival beyond the trial period (a parametric tail). The submitter provided feedback on the Initial Recommendation and expressed concern on the use of the lower 95% confidence interval is a poor choice to reflect overall survival. The EGP recognizes the value of the KM data, and that overall survival was found not to be clinically significant, which was represented by the lower 95% confidence interval. The upper 95% confidence interval was not chosen in an effort to maintain a conservative estimate while accounting for 40% cross-over, and adjustment of the results.

- Loss of treatment effect at end of trial follow-up. In a partitioned-survival model, time spent in the progression state is determined by (overall survival) - (progression-free survival). There is no clinical plausibility to see any benefit in either treatment group to be occurring in the progression state. Though individuals may accrue some benefit in the progression state (patients do not die immediately once treatment stops, they do continue to live), no incremental benefit should occur from one treatment to another. To minimize this, we used the setting provided by the submitter for loss of treatment effect at end of trial follow-up.
- Time horizon of 4 years, instead of 6-8 years. The Kaplan-Meier curve and the predicted model curves differ, and this difference becomes more pronounced as time goes on. As there is no further accrual of benefit beyond 4 years, from a modeling perspective, in order to reconcile the lack of fitting of the curves, it is prudent to truncate at 4 years time horizon. The submitter provided feedback on the Initial Recommendation and disagreed with the EGP on the use of a 4-year time horizon. The EGP feels a 4-year time horizon is appropriate for the reasons stated above.

Table 2. EGP Reanalysis for Best Case Estimates

Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICER (QALY)	Δ from baseline submitted ICER
<i>Baseline - submitter's base case (cross-over adjusted scenario)</i>	\$50,812	0.212	0.312	\$240,100	-----
EGP's Reanalysis for the Best Case Estimate					
<i>Lower bound</i>					
<i>Overall survival - parametric gamma curve</i>	\$50,812	0.212	0.312	\$240,100	-----
<i>Loss of treatment effect at end of trial follow-up</i>	\$50,357	0.185	0.264	\$272,020	\$31,920
<i>Time horizon - 4 years</i>	\$50,397	0.185	0.264	\$272,423	\$32,323
<i>Best case estimate of above three parameters</i>	\$50,812	0.173	0.244	\$289,467	\$49,367
<i>Upper bound</i>					
<i>Overall survival - KM lower 95% CI with gamma tail</i>	\$49,512	0.134	0.172	\$369,245	\$129,145
<i>Loss of treatment effect at end of trial follow-up</i>	\$50,357	0.185	0.264	\$272,020	\$31,920
<i>Time horizon - 4 years</i>	\$50,397	0.185	0.264	\$272,423	\$32,323

<i>Best case estimate of above three parameters</i>	\$49,247	0.116	0.140	\$425,651	\$185,551
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Overall the ICER is *higher* than what the submitter reported by: \$49,367 /QALY-\$185,551/QALY. The submitter provided feedback on pERC’s Initial Recommendation regarding the range provided by the EGR, that it does not properly reflect the true *range* of the ICER due to cumulative effects of combining several conservative scenarios. The EGP recognizes the conservative nature of these scenarios, but maintains that the three changes are not mutually exclusive, nor are they implausible, if combined. The submitter also stated in their feedback that the most conservative ICER overestimates the most likely mean ICER of bevacizumab, as the efficacy estimates in the reanalysis are lower than what was observed in the clinical trial. In response, the submitted efficacy in LYGs was 0.312 (3.7 months); the EGP had a range of 1.4 - 2.1 months. Given that trial data (and efficacy) is often better than real life, the EGP feels that the model estimates are not inconsistent. Again, the EGP recognizes the conservative nature of their approach, but does not feel it is inaccurate.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include using progression-free survival as a proxy for treatment duration and the usage rates (market uptake) of bevacizumab.

The BIA assumed that 90% of patients with PROC would be actively managed. The CGP identified that this is more likely to be between 70-80%, therefore the assumption in the base case made by the submitter is conservative.

1.6 Conclusions

The EGP’s best estimate of ΔC and ΔE for bevacizumab in combination with chemotherapy when compared to chemotherapy alone is:

- Between \$289,467/QALY and \$425,651/QALY
- Within this range, it is difficult to estimate where the ICER would lie, given the uncertainty around overall survival.
- The extra cost of bevacizumab is between \$49,247 and \$50,812. *Treatment duration, chemotherapy drugs used and cost of bevacizumab are the main drivers of cost.*
- The extra clinical effect of bevacizumab is between 0.116 and 0.173 QALYs (ΔE). *The type of curve used for overall survival, time horizon and adjustment for cross-over are the main factors of effectiveness.*

Overall conclusions of the submitted model:

- *It is challenging to assess the benefit of a drug in terms of overall survival when cross-over is allowed in the clinical trial. The lack of standard of chemotherapy mix also introduces some uncertainty around cost.*
- *The range provided by the EGP captures this uncertainty.*

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 Gynecologic 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) Platinum Resistant Ovarian Cancer. A full assessment of the clinical evidence of Bevacizumab (Avastin) Platinum Resistant 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*. Hoffmann-La Roche Limited as the primary data owner, did not agree to the disclosure of economic information, therefore, this information has been redacted in this Initial Economic 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.

REFERENCES

1. Poveda AM, Selle F, Hilpert F, et al. Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 10 2015;33(32):3836-3838.
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