PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Dabrafenib (Tafinlar) for Metastatic Melanoma

December 5, 2013

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by GlaxoSmithKline** compared dabrafenib to dacarbazine (DTIC) as a first line treatment for patients with advanced or metastatic BRAF positive melanoma based on the BREAK-3 trial. Dabrafenib is administered orally and DTIC is administered intravenously. No analysis was provided addressing the use of dabrafenib in the second line setting.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate as DTIC was previously considered the standard of care of patients with advanced melanoma at the time the BREAK-3 trial was designed. The Clinical Guidance Panel considered that vemurafenib is also a clinically relevant comparator as it has recently been approved by Health Canada for patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The Submitter also included an additional economic analysis of vemurafenib compared with dabrafenib, based on an indirect comparison analysis of the two agents. Vemurafenib is also administered orally. Both dabrafenib and vemurafenib are BRAF inhibitors.

Patients considered the following factors important in the review of dabrafenib, which are relevant to the economic analysis: life expectancy, quality of life, side effects and ease of use. The submitter incorporated progression-free and overall survival, quality of life and side effects in their economic model. A full summary of patient advocacy group input is provided in the pCODR Clinical Guidance Report.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for dabrafenib, and which are relevant to the economic analysis: ease of distribution and administration, patient compliance, sequential use of dabrafenib, and as a potential alternative treatment to vemurafenib. An economic analysis comparing dabrafenib to vemurafenib in the first-line setting was submitted by the manufacturer. Sequential use of dabrafenib was not considered in the economic analysis and there is a lack of data and uncertainty on the sequencing of new melanoma treatments in clinical practice. A full summary of PAG input is provided in the pCODR Clinical Guidance Report.

At the list price dabrafenib costs $42.22 and $63.33 per 50mg and 75 mg capsule, respectively. At the recommended daily dose of 150 mg twice daily (4 x 75 mg capsules per day), the cost of dabrafenib is $253 per day and the average cost per 28-day course is $7093.

At the list price, vemurafenib costs $46.54 per 240 mg tablet. At the recommended dose of 960 mg twice daily (8 tablets per day), the cost of vemurafenib is $372 per day. The average cost per 28-day course is $10,425. In the main analysis, the manufacturer assumed that in all jurisdictions, the price of vemurafenib is the same as the list price. The effective price of vemurafenib may however vary across jurisdictions and be lower than the list price if it is based upon a confidential price that is unknown to pCODR.

1.2 Summary of Results

Dabrafenib vs. DTIC

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $245,245 per QALY and $264,156 per QALY when dabrafenib is compared with DTIC in the first-line setting.

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 dabrafenib is between $74,452 and $74,471 (ΔC). The main cost driver is the cost of dabrafenib.
- the extra clinical effect of dabrafenib is between 0.343 and 0.375 life years, or 0.282 and 0.304 QALYs (ΔE). The main factors that influence ΔE are the relative efficacy on overall survival (OS) and progression-free survival (PFS) from the trial.

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

- Changing the HR for OS for dabrafenib from 0.57 to 1.0 or to 1.5 (based on BRIM-3 and upper CI) at 37 weeks and then decreasing the HR linearly to 1.00 by 43 weeks (where it remains for the rest of the projection), the extra cost of dabrafenib is between $74,471 and $74,493 ($\Delta C_1$) and the extra clinical effect is between 0.282 and 0.294 QALYs, which increases the estimated incremental cost-effectiveness ratio.
- Assuming the same utility between the two treatments, the extra clinical effect of dabrafenib is 0.296 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio.

The EGPs estimates were similar to the submitted estimates comparing dabrafenib with DTIC.

According to the economic analysis that was submitted by GlaxoSmithKline when dabrafenib is compared with DTIC:

- the extra cost of dabrafenib is $74,452 (ΔC). Costs considered in the analysis included cost of dabrafenib, cost of BRAF screening test and costs of follow-up during PFS and PPS.
- the extra clinical effect of dabrafenib is 0.375 life years or 0.304 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on OS and PFS from BREAK-3.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $245,245 per QALY or $198,640 per life year gained.

Note that sensitivity analysis conducted by GlaxoSmithKline explored uncertainty in OS by using the upper limit of the 95% CI for OS. In this sensitivity analysis, dabrafenib was dominated by DTIC (less benefit and more costly than DTIC).

Dabrafenib vs. vemurafenib

There is currently no head-to-head clinical trial comparing dabrafenib and vemurafenib. The manufacturer provided three different scenario analyses comparing dabrafenib and vemurafenib: a class effect analysis (assumed same efficacy and harm),

and two adjusted indirect treatment comparison (ITC) that estimated OS and PFS - an unrestricted analysis with different durations of follow-up from the trials, and a restricted analysis using the same duration of follow-up from the dabrafenib trial. Based on the available analyses and feedback from the pCODR Clinical Guidance Panel, the EGP used the class effect analysis, which assumed equal efficacy and harms for the two treatments, although significant uncertainty exists regarding true comparative effectiveness of dabrafenib and vemurafenib as there is no head-to-head trial.

The EGP's best estimate:

- the extra cost of dabrafenib is -$42,230 (ΔC). The cost saving is generated from the reduced cost of medication.
- the clinical effect of dabrafenib is assumed to be the same as vemurafenib based on input from the pCODR Clinical Guidance Panel and an indirect comparison provided by the manufacturer.

The EGPs estimates were similar to some of the submitted estimates although the manufacturer submitted a wide range of estimates for the comparison with vemurafenib.

For the other two scenarios where the efficacy and harms for the two treatments are different (no class effect), dabrafenib dominates vemurafenib in the unrestricted follow-up analysis (dabrafenib less costly and more effective than vemurafenib). In the restricted follow-up analysis, the cost effectiveness of vemurafenib vs. dafrafenib was $693,468 per QALY (vemurafenib more costly and more effectiveness than dabrafenib). Details of the two scenarios are listed below.

According to the economic analysis that was submitted by GlaxoSmithKline when dabrafenib is compared with vemurafenib (ITC unrestricted follow-up):

- the extra cost of dabrafenib is -$39,190 (ΔC). Costs considered in the analysis included cost of medication, cost of BRAF screening test and costs of follow-up during PFS and PPS.
- the extra clinical effect of dabrafenib is 0.052 LYs or 0.037 quality-adjusted life years (QALY) (ΔE). The clinical effect considered in the analysis was based on OS and PFS from an indirect comparison (ITC).

When dabrafenib is compared with vemurafenib in the ITC restricted follow-up analysis:

- the extra cost of dabrafenib is between -$39,064 (ΔC).
- the extra clinical effect of dabrafenib is -0.086 LYs or -0.056 quality-adjusted life years (QALY) (ΔE).

These estimates are dependent on the relative price of dabrafenib and vemurafenib and assume that the price of vemurafenib is the same as the list price in all jurisdictions. Further, the results of the ITC are highly uncertain and small changes in relative efficacy (ΔE) led to a wide range of the ICER estimate, depending on which of the approaches were used to compare dabrafenib and vemurafenib.

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 EGP's estimate differed from the submitter's estimates. The main reasons for differences in the comparison to DTIC is the length of declining benefits of dabrafenib for OS (37 to 43 weeks) and in the indirect comparison to vemurafenib, the quality of life assumption between the two treatments.

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

Yes. The primary concerns of the patients are life expectancy and quality of life, which were addressed in the model based on patient data from BREAK-3 trial. The government payer's perspective adopted in the submission did not consider employment and financial issues identified by the patient advocacy groups, although the perspective taken is appropriate for pCODR.

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 was adequate. The submitted model was used to estimate the impact of declining benefits and equal quality of life, which were listed in the EGP's re-analysis.

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 of the assumptions made in the submission were appropriate. The submitter added published literature and a survey with the Canadian oncologists to estimate the follow-up costs.

Modelling overall survival (OS) and progression-free survival (PFS) were two key clinical inputs for the economic evaluation where partitioned survival analysis was used. The submitted base case is based on the adjusted OS (using the RPSFT (rank preserving structural failure time) and IPE (iterative parameter estimation) methods to account for the pre-planned crossover nature of the clinical trial) that did not reach statistical significance. If actual OS is less than estimates (or HR closer to upper 95% CI), DTIC will dominate as stated in the submitter's sensitivity analysis (see section 2.1 for details). The open-labelled design might also bias the investigator-assessed PFS and quality of life.

For the indirect comparison between vemurafenib and dabrafenib, the submitter's assumptions on the relative efficacy of dabrafenib were appropriate but given that a head to head trial has not been conducted there is significant uncertainty in relative efficacy. For example, dabrafenib was more effective than vemurafenib in the unrestricted follow-up analysis, but less effective in the restricted follow-up analysis.

The model did not address dabrafenib as a second-line treatment, and as such the cost-effectiveness of dabrafenib as a second line treatment is unknown.

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 estimates of clinical effect and costs used in the submitted model are reasonable and adequate. However, there is considerable uncertainty in the costs and effects relative to vemurafenib. The conduct of sensitivity analysis to explore uncertainty was appropriately conducted.

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 dabrafenib over a three-year time horizon. The BIA contains assumptions regarding the number of new BRAF mutation positive patients and market share of first-line treatments (dabrafenib is assumed to only displace vemurafenib in the first year, and other therapies in subsequent years). The model results are most sensitive to the displacement of vemurafenib and treatment duration of dabrafenib and comparators.

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

The BIA did not consider the scenario where patients switch to dabrafenib after developed resistance to vemurafenib, which PAG was interested in. However, there is no clinical evidence to support this switch. In addition, dabrafenib as a second-line treatment was also not explored in the BIA. Trametinib was not identified as a relevant comparator in the BIA. Use of dabrafenib in combination with a MEK inhibitor such as trametinib was not considered in the BIA.

1.5 Future Research

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

The cost-effectiveness of dabrafenib as a second-line treatment of unresectable or metastatic melanoma can be explored in the scenario analysis, although no phase III RCT data is available at this stage.

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

There are no other economic evaluations of dabrafenib vs. DTIC, a complete validation of the provided inputs though independent research would be valuable. Also, a head-to-head trial comparing dabrafenib and vemurafenib would confirm the relative efficacy, toxicity and cost-effectiveness of dabrafenib. More precise data on incremental OS and PFS would reduce the degree of 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 Melanoma 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 dabrafenib (Tafinlar) for metastatic melanoma. A full assessment of the clinical evidence of dabrafenib (Tafinlar) for metastatic melanoma 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*. There was no information 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.

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