PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Trametinib (Mekinist) for Metastatic Melanoma

October 22, 2013

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The focus of the economic analysis submitted to pCODR by GlaxoSmithKline was to estimate the cost-effectiveness of trametinib as a monotherapy in the first-line treatment of patients with BRAF mutation positive unresectable or metastatic melanoma. This economic analysis undertook two comparisons: one based on a direct comparison of trametinib versus DTIC based on the METRIC trial;[1] and another based on an indirect treatment comparison of trametinib versus vemurafenib, which is a BRAF inhibitor. The specific indication was in "patients with advanced or metastatic BRAF V600E/K mutation-positive (histologically confirmed) melanoma with an ECOG performance status of 0 to 1, without a history of prior brain metastases, and without prior chemotherapy in the advanced or metastatic setting (i.e., first-line treatment)." This patient population reflects a sub-population of patients from the METRIC trial and a very similar population to the BRIM-3 trial,[2] and although the METRIC trial comparator was chemotherapy, the majority of chemotherapy patients received DTIC. The comparison against vemurafenib was undertaken based on two separate data cut-offs, one analysis presented vemurafenib data from 3.1 months of follow-up (restricted analysis); while a second analysis used 11.1 months of vemurafenib follow-up data (unrestricted analysis). DTIC is administered as an intravenous solution. An economic analysis of trametinib in the second-line setting was not submitted to pCODR, although patients who had previously been treated with chemotherapy for advanced were allowed in the METRIC trial.

According to the pCODR Clinical Guidance Panel (CGP), the comparison is against vemurafenib is more clinically relevant than the comparison against DTIC, although DTIC was considered an appropriate comparator at the time the METRIC trial was designed. The CGP indicated that the unrestricted analysis was more appropriate as this includes more follow-up data for the comparator treatment. The CGP also indicated that dabrafenib, another BRAF inhibitor would be an appropriate comparator. However, as dabrafenib has not received a recommendation from pERC, an economic analysis comparing trametinib to dabrafenib was not submitted to pCODR. Given the most appropriate comparison was determined to be against vemurafenib, the CGP agreed that the EGP concentrate on the first-line use (no prior chemotherapy) of trametinib.

Patients considered the following factors important in the review of trametinib: access to new efficacious treatment options, extension of life and expectation of less treatment side effects. The economic analysis takes into account overall survival (OS), and the difference in adverse event profile between trametinib, DTIC and vemurafenib in so far as costs associated with grade 3 or higher adverse events. It does not take into account the effects of the difference in adverse event profile on quality of life compared to either DTIC or vemurafenib. The expectation was that this difference would be captured in the overall quality-adjusted life-years (QALYs). 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 trametinib, and which are relevant to the economic analysis: head-to-head comparison against the current standard of treatment (vemurafenib), indication creep into the adjuvant setting and second line setting, monitoring costs, oral administration and the potential for sequential

dosing with new BRAF inhibitors coming to market. A full summary of PAG input is provided in the pCODR Clinical Guidance Report.

- PAG noted that current standard treatment for this population in many jurisdictions is vemurafenib and thus a head-to-head comparison of trametinib and vemurafenib monotherapy would be ideal. The manufacturer submitted an analysis based on an indirect comparison of trametinib and vemurafenib.
- PAG expressed concerns of indication creep into the adjuvant setting and second line setting. This factor has not been included in the submitted model, and could not be explored in an EGP sensitivity analysis given the lack of data to undertake this comparison.
- PAG noted that the once daily oral administration is one of the benefits of trametinib. Oral administration could not be considered in the economic evaluation of interest, as vemurafenib is also an orally administered drug. The frequency of dosing also could not be taken into account in the economic analysis.
- PAG identified the sequential use of trametinib and other oral BRAF or MEK inhibitors as a potential implementation barrier given the potential for increased costs. This factor has not been included in the submitted model, and could not be explored in an Economic Guidance Panel (EGP) sensitivity analysis given the lack of data and uncertainty around sequencing of these treatments in clinical practice.

At the list price, trametinib costs $72.50, $145.00 and $290.00 per 0.5, 1 and 2 mg tablets, respectively. The 1 mg tablet will however not be made available in Canada. At the recommended dose of 2 mg once daily, the cost of trametinib is $290 per day. The average cost per 28-day course is $8,120.

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

The EGP re-analysis and summary is primarily based on the initial data cut of the METRIC trial (used in the submission); although an additional scenario analysis based on the new data cut has also been undertaken. Data for the overall population from the new data cut-off suggests a lower OS HR than that reported in the earlier data cut which is line with what was seen in the vemurafenib study (BRIM-3). As BRIM3 included only patients who had not received prior chemotherapy, the comparison of trametinib and vemurafenib is based on the subpopulation from METRIC that had not received prior chemotherapy (n=176).

Trametinib vs. Vemurafenib

Although submitted results suggested trametinib was dominant (less costly, more effective) versus vemurafenib, EGP's best estimate – based on the re-analysis of the model submitted by GlaxoSmithKline Inc. - showed a high degree of uncertainty in the economic results and showed that trametinib may also be less costly and less effective than vemurafenib, with an incremental cost per QALY for vemurafenib vs. trametinib of between $104,663 and $391,708 (at the currently submitted prices).

The comparison of trametinib vs. vemurafenib is highly sensitive to the clinical efficacy results. The results of the submitted indirect treatment comparison favored vemurafenib over trametinib in terms of PFS. In terms of OS, the potential for treatment waning that was seen over 2 time points in the BRIM3 trial for vemurafenib resulted in favorable results for vemurafenib when using the results from the earlier time point from BRIM3 but favorable results for trametinib when using the results from the later time point. However, during the pCODR review period, new OS data from the METRIC trial have been made publically available, showing a lower HR than that indicated in the first cut off point. Although it is unclear as to whether the data are from a different population than that modeled by the manufacturer or whether the hazard ratio has been calculated in an appropriate way, given the switching from chemotherapy to trametinib, these results suggest a possible treatment waning effect for trametinib, in similar manner as for vemurafenib.

The incremental cost-effectiveness ratio was based on an estimate of the difference in cost (ΔC) and the difference in clinical effect (ΔE). The EGP's best estimate of:

- the difference in cost of trametinib compared with vemurafenib is a reduction of between $27,321 and $27,677. The cost of drug is the main driver of the cost difference.
- the difference in clinical effect of trametinib compared with vemurafenib is a reduction of between 0.071 and 0.261 QALYs. The difference in clinical effect is driven by the HRs for OS and PFS and the time in each state.

The EGP based these estimates on the model submitted by GlaxoSmithKline Inc. and reanalyses conducted by the EGP. The submitted model is based on a comparison of trametinib and DTIC from the initial data cut of one phase III trial (METRIC), and an indirect treatment comparison of one phase III trial of each of trametinib (METRIC) and vemurafenib (BRIM-3), both compared with DTIC. The primary outcome of the METRIC trial was PFS, while the BRIM-3 trial had co-primary outcomes of OS and PFS. The manufacturer's model relied on the adjustments of hazard ratios (HRs) for OS for both treatments, and assumptions around when trial data were censored and the projected data should begin. Based on the clinical data, the EGP and Methods team do not believe the indirect treatment comparison indicates that trametinib is more effective than vemurafenib and therefore the below range is based on this assumption:

The EGP's higher estimate of the range for the ICUR for vemurafenib vs. trametinib was $391,708. This assumed the following changes to the EGP reanalysis: use of the recently published data cut from the METRIC trial and the unrestricted population from the BRIM3 trial.

The EGP's lower estimate of the range for the ICUR for vemurafenib vs. trametinib was $104,663. This assumed the following changes to the EGP reanalysis: the time at which the hazard ratios for overall survival do not show a benefit over DTIC is 60 weeks.

The treatment time (for the comparative HRs) used in the EGP re-analysis was based on median follow-up time within the METRIC and BRIM3 trials and not the revised data cut-off point used by the manufacturer. Both an interim data analysis (termed the 'restricted analysis,' median follow-up 3.1 months) and a more recent analysis (termed the 'unrestricted analysis,' median follow-up 11.1 months) for the BRIM3 trial were presented. The EGP re-analyses used hazard ratios from both the restricted and unrestricted analysis of vemurafenib to attempt to account for treatment effect waning (compared with DTIC)

which was apparent between the first and last data cuts. The re-analysis indicates the uncertainty of the indirect comparison of the clinical data. The potential for a treatment waning effect was not taken into account in the trametinib arm as no analysis over different time points was undertaken to determine whether this would have occurred had the METRIC trial occurred over a similar trial length as BRIM3. It is unclear as to whether the most recent data cut provides comparable data for the modeled population, however the data indicate that the treatment effect has waned compared to the results at the initial data cut. Although there is the potential that the OS HR favoured vemurafenib in the EGP's re-analysis (given the extended trial time), the use of only shorter term, censored data in the manufacturers analysis may have favoured trametinib.

The EGP's best estimate is based on currently available evidence on the impact of trametinib on progression-free survival, overall survival and quality of life, as well as the current price of its comparator, vemurafenib. However, were the actual unit price of vemurafenib lower than the published unit price, the cost-effectiveness of trametinib (based on the EGP's re-analysis) would be substantially diminished unless the price of trametinib is also reduced. If the actual price of vemurafenib was the same as the submitted price of trametinib, the ICUR for vemurafenib vs. trametinib would be approximately $32,655 per QALY.

The EGPs estimates for trametinib vs. vemurafenib substantially differed from the submitted estimates.

According to the economic analysis that was submitted by GlaxoSmithKline Inc., when trametinib is compared with vemurafenib (unrestricted analysis):

- trametinib is less costly than vemurafenib (ΔC) by $27,956 over a 5 year horizon. Costs considered in the analysis included drug costs, costs associated with treatment of adverse events, diagnostic testing costs, and pre and post-progression background treatment costs.
- trametinib yielded 0.09 less progression-free life-years (PFLYs) than vemurafenib, but resulted in an extra 0.12 quality-adjusted life years and an extra 0.18 life years gained. The clinical effect considered in the analysis was based on overall survival and progression free survival data, as well as registry data, and projections based on adjusted trial data and assumptions.

The submitter estimated that the incremental cost-effectiveness ratio per progression-free life-years gained (ΔC/ΔE) is $[redacted] for vemurafenib compared to trametinib (trametinib costs less, but is less effective). (*Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines)*. The incremental cost-effectiveness ratio for life years gained and quality adjusted life years gained shows trametinib is dominant compared to vemurafenib (lower cost, more effective). It should be noted that using an earlier data cut of the comparator data (restricted analysis); although trametinib still dominates vemurafenib in cost per life year gained, it loses dominance in cost per quality adjusted life year (ICUR for vemurafenib compared to trametinib is greater than $4M).

The submitter reported that sensitivity analyses undertaken indicated that the ICURs are sensitive to the: hazard ratios applied, assumed start point for declining benefit, and assumed duration of benefits of trametinib on OS.

There is further uncertainty in the indirect treatment comparison as the HRs for OS for the trametinib vs. DTIC comparison are not statistically significant, while the results for

vemurafenib are statistically significant at both the 3.1 month follow-up and 11.1 month follow-up.

Trametinib vs. DTIC

Although the comparison against DTIC was not considered the most appropriate comparison, it was based on a direct comparison of trametinib vs. chemotherapy in patients with no brain metastases and no prior chemotherapy (the same population modelled by the manufacturer). The EGP undertook sensitivity analyses of the data by using the trial-reported HRs from the initial data cut, revising the RDI to 1, altering the time horizon to 3 years, and adjusting the time on trial to the median follow-up time for METRIC. The results of the EGP re-analysis were similar to the manufacturer's results (ICUR for trametinib vs. chemotherapy of $155,584 to $248,982 per QALY). Were the OS HR from the most recent data cut to be used, the ICUR would be expected to be higher. Neither the PFS nor OS hazard ratios for this subpopulation were statistically significant.

According to the economic analysis submitted by GlaxoSmithKline Inc. comparing trametinib with DTIC (based on the METRIC trial):

- trametinib is more costly than DTIC (ΔC) by $68,145 over a 5 year horizon. Costs considered in the analysis included drug costs, costs associated with treatment of adverse events, diagnostic testing costs, and pre and post-progression background treatment costs.
- trametinib yielded 0.2524 more progression-free life-years (PFLYs) than DTIC, as well as an extra 0.4015 quality-adjusted life years and an extra 0.5466 life years gained over a 5 year horizon. The clinical effect considered in the analysis was based on overall survival and progression free survival data, as well as registry data, and projections based on adjusted trial data and assumptions.

The submitter estimated that the incremental cost-effectiveness ratio per progression-free life-years gained (ΔC/ΔE) is $[redacted] for trametinib compared with DTIC. (*Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines).* The incremental cost-effectiveness ratio for trametinib compared to DTIC is $124,661 per life year gained, and $169,704 per QALY gained.

An exploratory sensitivity analysis of trametinib vs. DTIC for the population who had received 1 course of prior chemotherapy (n=97) was undertaken (as per the inclusion criteria for the METRIC study). The results for this population were very similar to the population with no prior chemotherapy (ICUR: $155,731 to $244,353 per QALY). As for the subpopulation that received no prior chemotherapy, the OS HR for the subpopulation that received prior chemotherapy was not statistically significant.

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 estimate is based on a re-analysis using the reported trial-based hazard ratios. Trial data from the various data cut-offs have been incorporated in the EGP re-analysis.

This takes into account that the BRIM3 trial has more than twice the follow-up compared the METRIC trial (based on the manufacturer's modeled data). The EGP, with guidance from the Methods team, determined that the trial-reported hazard ratios for vemurafenib and trametinib were more appropriate than the adjusted values used in the manufacturer's analysis to the trial-based values. Only data adjusted using the RPSFTM method have been determined to be appropriate. Data were projected from the study completion to 5 years although a sensitivity analysis was undertaken based on a 3-year time horizon following feedback from the CGP. The manufacturer used adjusted progression-free survival (PFS) and OS trial data from the same data points, and forecasts data from 30 weeks to 5 years. The EGP also used data from a more recent (later) data cut of the METRIC trial to conduct a scenario analysis. The more recent data indicates that the hazard ratio of trametinib vs. DTIC has diminished over time.

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

Patient advocacy group input indicated patients considered survival, toxicity and quality of life as being of primary importance to the patients. Overall survival and progression-free survival were looked at in this economic evaluation, as was quality of life. While adverse events were assessed in monetary terms, the impact of these adverse events on quality of life was not assessed.

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

Yes. Although the submitted partitioned-survival analyses based on restricted and unrestricted analysis of the comparator treatment may not be entirely appropriate, the model is adequate to assess the cost-effectiveness of trametinib vs. vemurafenib in this setting.

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?

A major assumption made in the manufacturer's model is that there is overall survival benefit in the indirect comparison of trametinib vs. vemurafenib in both its restricted and unrestricted analyses which favours trametinib. This does not appear to be supported by trial data. The manufacturer's adjusted values and time at which clinical benefit was seen for both trametinib and vemurafenib appeared biased towards trametinib.

The manufacturer's model assumed a time horizon of 5 years. Given the short follow-up time for trametinib (4.9 months), extrapolating the data out to 5 years is fraught with considerable uncertainty. The CGP indicated that a time horizon of 3 years could also be appropriate in this patient population.

The utility values used in the model differ to other reported utility values in the post-progression stage.

Based on EGP reanalysis of the data, trametinib may not be as effective as vemurafenib, although it is likely to be less costly based on list prices of the two drugs. However, the effective price of vemurafenib may vary across jurisdictions and be lower than the list price if it is based upon a confidential price that is unknown to pCODR.

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 cost data used seemed adequate and the EGP would have used similar data (possibly with the exception of the cost attributed to end of life). However, within the model structure, some of the adjusted HRs used did not appear appropriate given the differences from the reported clinical trial results. Estimates of the long-term survival gains with trametinib were uncertain due to an assumption relating to the length of time that benefit was expected for each of the treatments in the indirect treatment comparison. EGP would have used individual level data to estimate transition probabilities among the three Markov states and would have conducted a Markov model instead of survival partitioned model, which might have accounted for differences in risk of death before and after disease progression.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The manufacturer submitted a budget impact analysis (BIA) that was not specific to any Canadian public drug plan which estimates of the increased costs for the three years with two alternate scenarios: a 'reference scenario' which assumes that trametinib is not available, and a 'new drug scenario' which assumes that trametinib is available. The budget impact analysis provided estimates of the increased costs for the three years subsequent to the listing of trametinib as a first-line treatment for patients with BRAF mutation positive unresectable or metastatic. The key variables included in the manufacturer's BIA are: treatment cost, proportion of patients that receive trametinib first-line as monotherapy, comparator treatments, market share estimates, and the proportion of population covered by a provincial public drug plan. The manufacturer's submitted six one-way sensitivity analyses varying target population size, included comparator treatments and market expansion, and reported that the results were most sensitive to market expansion assumptions.

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

The model structure of the BIA was appropriate. The key limitations of the submitted budget impact analysis relate to the limited data to support the assumptions relating to the market share of trametinib, as well as and uncertainty around the treatment duration.

1.5 Future Research

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

An economic model which investigated the full effect of the comparator treatment, taking into account the potential for treatment waning over time, as seen in the BRIM3 trial in a single analysis would have been helpful. An economic model that provides the opportunity to adjust the movement of patients from pre-progression to post-progression to death would have enabled more accurate estimation of cost-effectiveness estimates.

A more recent data cut of the METRIC trial appears to have been made available in May 2013. Some of these data have been published in the most recent Product Monograph for trametinib. An economic evaluation with the inclusion of new data for the modelled population would have been more relevant.

Is there economic research that could be conducted in the future that would provide valuable information related to trametinib for the first-line treatment of advanced or metastatic melanoma?

A direct comparison of trametinib against vemurafenib would provide a much more appropriate comparison than the current indirect treatment comparison which itself has inherent uncertainties.

Dabrafenib may also be a relevant comparator in the future as this submission is currently under review by pERC at the present time; and thus was not included in the submitted economic analysis. However, trials evaluating dabrafenib monotherapy are available and an indirect treatment comparison against trametinib would have been a potentially relevant analysis to have undertaken.

Economic analyses evaluating trametinib in combination with a BRAF inhibitor were not conducted. Trials evaluating these combinations are currently ongoing but could provide valuable information in the future.

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 Final 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 trametinib (Mekinist) for unresectable or metastatic melanoma. A full assessment of the clinical evidence of trametinib (Mekinist) for unresectable or 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*. 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 Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical 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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