PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Dabrafenib (Tafinlar) for Metastatic Melanoma

December 5, 2013

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Tafinlar™ (dabrafenib); metastatic melanoma
Role in Review (Submitter and/or Manufacturer):	Submitter
Organization Providing Feedback	GlaxoSmithKline Inc.

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

___ agrees _X__ agrees in part ____ disagree

Please explain why the Submitter *agrees, agrees in part or disagrees with the initial recommendation.*

GSK agrees only in part with the initial recommendation due to the following:

1. The wording regarding use in patients with brain metastases is ambiguous, which may lead to misinterpretation of pERC's intent, and it also does not reflect the BREAK-MB study population (i.e., limits the use of dabrafenib to patients with stable vs. asymptomatic brain metastases per BREAK-MB). Both of these could result in a lack of appropriate access to dabrafenib for patients with brain metastases.

2. The recommendation to limit the use of dabrafenib to patients with BRAF V600E-mutation positive unresectable or metastatic melanoma only is not consistent with the data from 2 well-controlled phase 2 studies, BREAK-2 and BREAK-MB. The data from these 2 studies constitutes the largest prospectively selected sample of melanoma patients whose tumour harbors the V600K.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

___ Support conversion to final recommendation.	__X_ Do not support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.	Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
1	pERC Recommendation	Paragraph 1, line 5-6	Change wording from, "If brain metastases are present, they should be stable" to "If brain metastases are present, they should be asymptomatic (i.e. free of neurological symptoms) and can be either previously treated or untreated"

The totality of evidence generated in BREAK-MB, with respect to overall response rate, duration of response, progression free survival (PFS) and overall survival (OS) support the clinical benefit of dabrafenib in patients with V600-mutation positive metastatic melanoma to brain, with or without prior local treatment. The pERC's recommendation should not be restricted to patients with only stable brain metastases, rather it should reflect the patient population enrolled in BREAK-MB.

- BREAK-MB, the largest prospective study undertaken in patients with melanoma and brain metastases, is a key supportive study which provides data in this important subset of patients not typically represented in clinical trials. Since no active systemic therapy currently available for the treatment of patients with brain metastases that addresses both local and systemic disease, BREAK-MB was conducted as a single-arm study as there is no clear comparator. Chemotherapies, such as temozolamide, are largely ineffective in this population and associated with a particularly short survival[1]; while local therapies do not address metastases outside the brain. A randomized trial was therefore not performed due to ethical considerations. A two-cohort design was deemed as most appropriate in order to evaluate the efficacy and safety of dabrafenib in two sub-populations. BREAK-MB enrolled 172 patients with BRAF V600E or V600K-mutation positive melanoma with asymptomatic (i.e. free of neurological symptoms) brain metastases; 89 in Cohort A (no previous local treatment for brain metastases) and 83 in Cohort B (had disease progression in the brain after surgery, whole-brain radiotherapy, or stereotactic radiosurgery). [6]
- In BREAK-3, patients with CNS metastases were included if they were without evidence of active CNS metastases for >3 months after surgery or stereotactic radiosurgery. As such only 6 patients with CNS lesions (4 on the dabrafenib arm and 2 on the DTIC arm) were enrolled in the trial.
- In BREAK-MB, dabrafenib provided a clear and meaningful benefit as demonstrated by the primary endpoint of confirmed overall intracranial response rate [39.2% (95% CI: 28.0-51.2%) in Cohort A and 30.8% (95% CI: 19.9-43.4%) in Cohort B, in V600E patients). Similarly, the confirmed overall response rate [37.8% (95% CI: 26.8-49.9%) in Cohort A and 30.8% (95% CI: 19.9-43.5% in Cohort B, in V600E patients), which included evaluation of both intracranial and extracranial target lesions, indicates a comparable efficacy of dabrafenib against intracranial- and extracranial melanoma lesions. In addition, the time to onset of response was short, with a median time of 4.1 weeks in Cohort A and 4.2 weeks in Cohort B. Responses were durable, with a median duration of intracranial response of 20.1 weeks in Cohort A and 28.1 weeks in Cohort B. The rapid onset of response and duration of response observed suggest that dabrafenib has a clinically meaningful benefit in this population. Furthermore, the median PFS of over 4 months (Cohort A: 16.1 weeks; Cohort B: 16.6 weeks) and the median OS of over 7 months (Cohort A: 33.1 weeks; Cohort B: 31.4 weeks) compare favorably to the efficacy of any systemic treatment studied in this melanoma population to date.[2, 3]

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
1	pERC Recommendation	Paragraph 1, lines 3-4	Change wording from "Funding should be for first-line treatment of patients with BRAF V600E mutant-positive unresectable or metastatic melanoma" to ""Funding should be for first-line treatment of patients with BRAF V600 mutant-positive unresectable or metastatic melanoma"

The totality of evidence generated in BRAF V600K patients supports dabrafenib's efficacy for a broad reimbursement criteria (i.e., V600 vs. V600E). The pERC's recommendation should not be restricted to patients with only BRAF V600E-mutation.

- Based upon emerging data from the first time in human study (BRF112680) demonstrating differences in clinical activity between V600E and V600K-mutation positive melanoma, GSK designed 2 well-controlled phase 2 studies, BREAK-2 and BREAK-MB, such that the V600K-mutation positive melanoma were prospectively selected in both studies.
- Given the low frequency of V600 mutations other than V600E, studying these prospectively in a randomized clinical trial setting to obtain meaningful estimates of time to event endpoints such as median PFS would not have been feasible.
- The BREAK-3 study was designed to mirror that of the pivotal trial (BRIM-3) for the competitor compound vemurafenib, which only prospectively enrolled V600E patients. It was only by retrospective sequencing that 19 out of 220 patients in the BRIM-3 trial were discovered to be V600K (vemurafenib Product Monograph).
- To date, 49 patients with BRAF V600K-mutation positive melanoma have been studied across the dabrafenib monotherapy program. This is the largest prospectively selected sample of patients whose tumour harbors the V600K activating mutation sub-type.
- In BREAK-2, the overall disease control rate in V600K patients was 57%; 13% achieved a confirmed response rate (95% CI: 0-28.7%) and 44% had stable diseases for a minimum of 12 weeks.[5] This response rate is higher than that reported for historical treatment options such as DTIC (10-12%) and offers a more durable median duration of response of 5.3 months (95% CI: 3.7-6.8 months) versus 1.6 months previously reported for DTIC.[5] In addition, the response rate for DTIC has also been shown to be lower in the V600K population; V600K patients on the DTIC arm of BRIM-3 had a response rate of only 4%.[4] Nevertheless, as demonstrated in BREAK-2, V600K patients do benefit from treatment with dabrafenib, as evidenced by 57% of patients achieving disease control, a median PFS estimate of 4.5 months (95% CI: 2.6-6.2 months) and an OS rate similar to V600E patients (13.1 months vs. 12.9 months). [5]
- In BREAK-MB, the overall disease control rate in V600K patients was 46.7% in Cohort A and 50.0% in Cohort B.[6] In a population where the historical OS in patients with brain metastases (regardless of mutation status) is approximately 3-5 months[7], an OS benefit of 16.3 weeks (95% CI: 6.9-22.4 weeks) in Cohort A and 21.9 weeks (95% CI: 15.3-NR weeks) in Cohort B for patients specifically with the V600K mutation was seen with dabrafenib.[6]
- In conclusion, lower incident V600 mutation sub-types have not been studied prospectively in randomized clinical trials of any approved compound. GSK has however generated substantial prospective data in the V600K subtype in 2 well-controlled phase 2 studies. The totality of this evidence supports efficacy for a broad reimbursement criteria (i.e. V600 vs. V600E) for BRAF mutant metastatic melanoma. GSK believes that the evidence generated with dabrafenib, with respect to overall disease control, duration of response, PFS and OS supports the clinical benefit in a V600 population as approved by Health Canada. BRAF mutation validated tests currently in use do not necessarily enable prescribers to differentiate different sub-types. As such GSK is concerned that if the recommendation for dabrafenib is restricted to V600E specifically, it may delay a patient's ability to receive therapy. Due to the time currently required for BRAF testing, approximately 2-8 weeks elapse between a diagnosis of metastatic melanoma and receipt of the first dose of targeted therapy. Requiring dabrafenib patients to be V600E positive may add further delays given that that some Canadian testing sites do not identify the BRAF V600 mutation subtype and additional sequencing, and hence time, would be required.
- In addition, the statement " Because pERC recommended funding for dabrafenib only in patients with V600E-mutation positive melanoma, funding for dabrafenib should not be made available unless funding for the diagnostic testing of BRAF V600E mutations is also available" will limit the choice of treatment options for patients. For example, in Ontario the laboratory testing samples only reports "V600" positive, while in BC the testing laboratory reports "V600E/K" regardless of the specific mutation finding.

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

- Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.
- Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.
- The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)
- At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.
- Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.
- Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts

and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.

References

1. Agarwala SS, Kirkwood JM, Gore M, et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: A Phase II study. J Clin Oncol 2004;22:2101-7.

2. Carlino MS, Fogarty GB, and Long GV. Treatment of Melanoma Brain Metastases: A New Paradigm. Cancer J. 2012 Mar-Apr;18(2):208-12.

3. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012;13:459-65.

4. McArthur G, Hauschild A., Robert C., et al, Efficacy of vemurafenib in BRAFV600K mutation positive melanoma disease-results from the phase 3 clinical study BRIM3. Pigment Cell and Melanoma Research 2012 25:6 (871).

5. Acierto PA, Minor D, Ribas A, et al. Phase II Trial (BREAK-2) of the BRAF Inhibitor Dabrafenib (GSK2118436) in Patients With Metastatic Melanoma. J Clin Oncol. 2013 Sep 10; 31(26):3205-3211. **GlaxoSmithKline.** Module 2.5 Clinical Overview. 2012.

6. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Nov;13(11):1087-95.

7. Davies MA, Liu P, McIntyre S, et al. Prognostic factors for survival in melanoma patients with brain metastases. Cancer 2011;117:1687-96.