pan-Canadian Oncology Drug Review

Patient Advocacy Group Feedback on a pCODR Expert Review Committee Initial Recommendation

Dabrafenib (Tafinlar) and Trametinib (Mekinist) Non-Small Cell Lung Cancer

Lung Cancer Canada

November 2, 2017

1 Feedback on pERC Initial Recommendation

Name of the drug indication(s):	dabrafenib plus trametinib in combination for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation and who have been previously treated with chemotherapy
Name of registered patient group:	Lung Cancer Canada

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

1.1 Comments on the Initial Recommendation

a) Please indicate if the patient group agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part __X__ disagree

Please explain why the patient group agrees, agrees in part or disagrees with the initial recommendation.

Lung Cancer Canada Patient Group Response to pCODR pERC Initial Recommendation for Dabrafenib +Trametinib for BRAF V600 positive NSCLC

Lung Cancer Canada vehemently disagrees with pERC's assessment that dabrafenib & trametinib for BRAF V600 positive NSCLC only partially aligns with patient values. We believe that it completely aligns with patient values in all aspects.

b) Notwithstanding the feedback provided in part a) above, please indicate if the patient group would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

____ Support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.

__X__ Do not support conversion to final recommendation.
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

1.2 Comments Related to Patient Group Input

Please provide feedback on any issues not adequately addressed in the initial recommendation based on patient group input provided at the outset of the review on outcomes or issues important to patients that were identified in the submitted patient input. Please note that new evidence will be not considered during 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 providing is eligible for a Resubmission, please contact the pCODR program.

Examples of issues to consider include: what are the impacts of the condition on patients' daily living? Are the needs of patients being met by existing therapies? Are there unmet needs? Will the agents included in this recommendation affect the lives of patients? Do they have any disadvantages? Stakeholders may also consider other factors not listed here.

Page Number	Section Title	Paragraph, Line Number	Comments related to initial patient group input
Page 3	**pCODR pERC Initial Recommendation:** The Committee was not satisfied that the available evidence demonstrated a net overall clinical benefit of treatment with this intervention. pERC noted that an objective tumour response was observed with dabrafenib plus trametinb; however on its own this was not considered to be sufficient evidence of clinical effectiveness. Additionally, investigator-assessed, complete responses were observed in only	**Paragraph 2 and Sentence 2**	As a patient group, LCC disagrees with this assessment. Patients desire treatment options that work and that definition of "work" includes acknowledgement by physicians and other expert groups. In the case of dabrafenib & trametinib both groups agree in the efficacy of this drug. Our own Medical Advisory Committee believes that "The response rate of dabrafenib + trametinib (D&T) is 63.2% in comparison to 12% for docetaxel. This response rate is triple of that observed in chemotherapy." The highly significant overall response rate aligns with that of other targeted therapies and is also acknowledged by the pERC Clinical Guidance Panel. [Pg. 15, Clinical Guidance Report]. pERC also used the lack of complete response and no patients "based on the IRC assessment, experienced a complete response and ORR was driven exclusively by partial response. [Pg. 3 of Clinical Guidance Report] (Incidentally, in our submission we highlight the stories of four patients who did observe a complete response.) Lung Cancer Canada reminds pERC that lung cancer is a deadly cancer. It has a 17% five-year

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	4% of patients, with the remainder reporting only partial responses.		survival rate and is the cancer that takes the lives of more Canadians than any other cancer. Complete responses are still rare and the lack or rarity of a complete response is not a reasonable argument against the efficacy of a treatment. Lung Cancer Canada believes that this data completely aligns with patient values.
Page 6	**Initial pCODR pERC Recommendation:** pERC further considered the feasibility of conducting and RCT in this setting. Although pERC acknowledged that the incidence of BRAF V600 mutation-positive NSCLC is low, the incidence and prevalence of lung cancer is high, and conducting a multi-centre RCT with appropriate comparators would be feasible.	**Paragraph 3, Sentence 1**	Lung Cancer Canada feels that pERC's belief in the feasibility of a RCT does not align with patient values. This is not a reasonable, ethical or feasible request. First, it suggests an overestimation of the size of the BRAF V600 positive patient population. It is recognized that BRAF mutations in lung cancer are extremely rare - BRAF v600E mutations are even rarer. As noted from the LCC Medical Advisory Board clinician submission: "It is estimated that 28,400 Canadians will be diagnosed with lung cancer this year and 20,800 will die of the disease. From published series, we estimate that between 1-4% of metastatic NSCLC patients will have a BRAF mutations and half of those will be V600 mutations that are relevant to this application. If you presume that all 20,800 patients who die of the disease have metastatic disease given the median survival of stage IV lung cancer is about 12 months (with treatment), then 415 patients will have V600E mutations. This does not account for the fact that less than half of patients with metastatic lung cancer receive any treatment and less than half of those patients receive second line therapy or beyond. A more realistic estimate would be around 100

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			patients per year with the above information." Given the rarity of this mutation, the feasibility and completing a RCT in a timely or even reasonable fashion is not possible. In addition, the PAG also acknowledge that "many experts would question the ethics of randomized trials of dabrafenib and trametinib compared with chemotherapy in BRAF mutated NSCLC in the second line setting." [Clinical Guidance Report, Interpretation Pg. 9, first paragraph]. Conducting a RCT would pose tremendous and unreasonable recruitment challenges. As a reminder, this single arm trial of 56 patients took 13 months across 30 centres in 9 countries on 3 continents. It will take a RCT many years, beyond what is reasonable for that trial to complete. Statisticians can provide the appropriate calculations. Lung Cancer Canada believes that it is unconscionable to expect BRAF positive lung cancer patients to wait in light of data which experts agree have strong anti-tumour activity. If a RCT is a demand for reimbursement, BRAF V600 mutation positive Canadian lung cancer patients will never have access to this treatment. It runs contrary to the core oncology principle of personalized medicine and discriminates against lung cancer patients that have actionable mutations with small numbers. This action is contrary to patient values.
Page 9	**Initial Recommendation:** pERC highlighted that there is a continued need for more effective treatment options	**Last paragraph**	Immunotherapies represent a large step forward in lung cancer treatment. However, Lung Cancer Canada believes that this pERC decision which prioritizes immunotherapy over dabrafenib and trametinib is against scientific principle and patient values.

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	for patients; however, given the availability of immunotherapies (nivolumab and pembrolizumab), pERC agreed that patients do have other treatment options.		In the era of personalized medicine, experts including the NCCN and ASCO, agree that patients with an actionable mutation should be given a targeted therapy before immunotherapy where one exists. pERC's own recommendation for Keytruda clearly states that the immunotherapy should be used after the targeted therapy options. By denying D&T in favour of other options, pERC is supporting a treatment approaching that is contrary to recognized guidelines and best practice, and contrary to patient values.
Page 6	**Initial pCODR pERC Recommendation:** Patient-reported outcomes: No information of quality of life. pERC was unable to deliberate on the impact of dabrafenib plus trametinib of patients' QoL, as these data were not collected in the trial.	**Paragraph 4**	Lung Cancer Canada disagrees that there is "no information on quality of life". While "a measure of Quality of Life (QoL) was not reported in the main trial results" due to the single arm trial design, Lung Cancer Canada provided qualitative and semi-quantitative information on QoL in the submission. As a reminder, Lung Cancer Canada included the thoughts of nine dabrafenib & trametinib patients and nine caregivers in the submission. The results indicate that the dabrafenib & trametinib combination is a highly tolerable drug. Dose adjustments were able to resolve side effect issues. "After adjustments, side effects were reported to be none/low by 8 of the 11 patients and caregiver respondents on combination therapy." [Lung Cancer Canada Patient Group Submission]. Additionally patients reported that treatment with dabrafenib & trametinib resolved the symptoms of lung cancer. Our submission indicated that "One patient said he went from feeling tired, shortness of breath and coughing 200-500 times per day prior to receiving treatment, to feeling great with no coughing, symptoms or side effects. One respondent stated: "After nine days it was 'night and day'". For

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			another, within two weeks of starting dabrafenib & trametinib her breathing was better and her coughing stopped. "The results were dramatic," she said. Another respondent said he found a return of the same energy levels he had before being diagnosed." [Initial Clinical Guidance Report, pg. 25]. One patient was able to return to work and enjoy vacations. These reports indicates a high quality of life for patients treated with dabrafenib & trametinib. Patients report that they are able to "live well", "live better", "live longer" and thus highly aligns with patient values. We recognize this data is anecdotal and non-comparative. However, given the single arm trial design, any QoL data generated would still have been non-comparative. Our evidence highlights real-world themes and is evidence of the strength and the role of real-world evidence in evaluating new medications. Due to the small number of BRAF V600 positive NSCLC patients, this trial had 56 patients. It took 13 months to recruit. Our submission was able to include the voices of 8 patients and 8 caregivers, all of whom Lung Cancer Canada was able to find within a short period of time. As lung cancer targeted therapies evolve, more molecular targets are found and treatment becomes more precise, it is reasonable to believe that the patient population who may benefit from each treatment may be small and select. Once Phase 2 results are released, real-world evidence may be the only way - most appropriate way - to evaluate true benefit. If health technology assessment does not evolve to embrace and recognize the opportunities and patient outcomes made possible by these innovations,

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			and consistently insist on phase 3 data, Canadian patient outcomes will lag behind other countries. Waiting is not an option for lung cancer patients. Using current HTA evaluative standards, patients like BRAF V600 lung cancer patients will be forever waiting for a treatment that will never come. pERC MUST reconsider this decision.

1.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

pCODR Patient Group Feedback on a pERC Initial Recommendation

About Completing This Template

pCODR invites those registered patient groups that provided input on the drug under review **prior** to deliberation by the pCODR Expert Review Committee (pERC), to also provide feedback and comments on the initial recommendation made by pERC. (See www.cadth.ca/pcodr 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.cadth.ca/pcodr 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 patient groups agree or disagree 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, including registered patient groups, agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation two (2) Business Days after the end of the feedback deadline date. 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

a) Only registered patient groups that provided input at the beginning of the review of the drug can provide feedback on the initial recommendation.

- Please note that only one submission per patient group is permitted. This applies to those groups with both national and provincial / territorial offices; only one submission for the entire patient group will be accepted. If more than one submission is made, only the first submission will be considered.
- Individual patients should contact a patient group that is representative of their condition to have their input added to that of the group. If there is no patient group for the particular tumour, patients should contact pCODR for direction at pcodrinfo@cadth.ca.

b) 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 during this part of the review process; however, it may be eligible for a Resubmission.

c) The template for providing *pCODR Patient Group Feedback on a pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. Patient groups 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 to their group. Similarly, groups should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the initial pERC recommendations **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.

f) 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.

g) References to support comments may be provided separately; however, these cannot be new references. New evidence is not considered during 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.

h) The comments must be submitted via a Microsoft Word (not PDF) document by logging into www.cadth.ca/pcodr and selecting "Submit Feedback" by the posted deadline date.

i) Patient group feedback must be submitted to pCODR by **5 P.M. Eastern Time** on the day of the posted deadline.

j) If you have any questions about the feedback process, please e-mail pcodrinfo@cadth.ca. For more information regarding patient input into the pCODR drug review process, see the *pCODR Patient Engagement Guide*. Should you have any questions about completing this form, please email pcodrinfo@cadth.ca

Note: Submitted feedback is publicly posted and also may be used in other documents available to the public. The confidentiality of any submitted information at this stage of the review cannot be guaranteed.