CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

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

November 2, 2017

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Dabrafenib (Tafinlar) and Trametinib (Mekinist) for metastatic BRAF+ NSCLC patients after treatment with chemotherapy
Role in Review:	Submitter and Manufacturer
Organization Providing Feedback:	Novartis Pharmaceuticals Canada

1.0 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 ____ agrees in part X disagree

Novartis Pharmaceuticals Canada does not agree with the pERC initial recommendation as it pertains to the unmet medical need, the clinical evidence provided by Study BRF113928, and the feasibility of a Phase III clinical trial, which also seems to be in conflict with the Clinical Guidance Report (CGR).

1) Unmet medical need in the BRAF$^+$ NSCLC patient population

There remains a need to identify new therapeutic targets to advance treatment options in those patients who are EGFR wild type, or ALK negative, including BRAFV600+ NSCLC patients, as mentioned in the CGR.

In the initial recommendation, pERC is uncertain whether dabrafenib plus trametinib addresses an unmet medical need, as Tafinlar and Mekinist combination is the only treatment that specifically targets the BRAF V600E mutation in NSCLC. Current available treatments (i.e. chemotherapy and immunotherapies) have not been studied in this population with a very specific driver-mutation and have consequently not demonstrated proven efficacy in BRAF V600$^+$ NSCLC.

To date, the enrollment of patients in the Novartis patient support program reflects the expected prevalence of this mutation in the Canadian BRAF$^+$ NSCLC patient population, and underscores the unmet need of this population in a context of other available therapies and novel treatments, such as chemotherapy and immunotherapies.

2) Clinical evidence provided by BRF113928

In the recommendation, pERC stated that "patients with BRAF V600E mutation currently have treatment options following treatment with systemic chemotherapy". To date, there is no clinical trial evidence on the effect of immunotherapies in BRAF-mutated, advanced NSCLC. The experience in other mutation-driven NSCLC subsets such as EGFR and C-MET suggests that before such data are available, optimal treatment likely involves targeted therapy. Accordingly, the newly updated NCCN guidelines recommend treatment of BRAF V600$^+$ NSCLC with the dabrafenib and trametinib combination, as "the data in the second-line setting suggests that immunotherapy is less effective, irrespective of PD-L1 expression, in tumors with actionable mutations".[1]

Although immunotherapies have garnered attention for their antitumour activity in multiple tumour types, including NSCLC, caution must be applied when extrapolating these results into small patient populations with identified driver mutations or gene alterations. Several Phase III Randomized Clinical Trials (RCT) that have

evaluated immunotherapies versus chemotherapy as second- or subsequent-line therapy in advanced NSCLC, and subgroup analyses, found no clinical benefit in patients with EGFR and ALK alterations[2-4]. Consequently, the preferred treatment for these patients involve targeted therapies. A retrospective review looking at PD-L1 expression status amongst 81 patients with C-MET alteration presented at the 2017 ASCO meeting, demonstrated that while a relatively high proportion of these patients have tumours expressing high PD-L1 levels, which has been associated with higher response to pembrolizumab in advanced NSCLC[5], their response to immune checkpoint inhibitors appears to be poor – even in patients with high PD-L1 expression[6]. A second presentation focusing on the C-MET mutated advanced NSCLC patient population demonstrated that for these patients, treatment with an anti-C-MET targeted therapy resulted in significant survival benefit compared to treatment with non-targeted therapy[7], reiterating findings of other mutation-driven advanced NSCLC populations.

As stated in the CGR, the ORR and PFS in Study BRF113928 are "impressive" (66.7% for ORR, 10.2 months for PFS and 18.2 months OS respectively) and "these data suggest much greater clinical benefit than what would be expected from standard second-line therapies, although this represents a select group of patients". It is also mentioned that "the efficacy of docetaxel or immunotherapy in these patients would certainly not be expected to approach the efficacy data observed in the Study BRF113928, which does show major activity of dabrafenib and trametinib".

The pERC noted that "ORR is an uncertain surrogate for OS". While ORR was the primary end-point of the BRF113928 Study, PFS and OS were key secondary end-points. A recent meta-analysis of 14 trials in advanced NSCLC conducted by the FDA demonstrated that ORR was strongly correlated with OS (R2=0.74).[8] Additionally, time to progression, which is closely related to PFS, has been shown to be associated with OS and post-progression survival among advanced BRAF V600^{+} NSCLC patients who were treated with a targeted therapy.[9] Thus, in the absence of mature OS data, ORR or PFS are being considered as viable surrogate endpoints.

3) Feasibility of a Phase III randomized clinical trial

pERC believes that "conducting a multi-center RCT with appropriate comparators would be feasible" despite that "given the small number of patients with BRAF V600+, registered clinicians are not anticipating that RCTs will be conducted in this setting", as mentioned in the initial recommendation.

Novartis respectfully disagrees with pERC statement and Lung cancer experts have indicated that recruitment into a Phase III RCT would be hindered by the lack of equipoise in a study comparing the combination regimen to current standard of care in BRAF V600^{+} mutation NSCLC. In addition, as stated in the CGR, "many experts would question the ethics of randomized trials of dabrafenib plus trametinib compared to chemotherapy in BRAF V600^{+} NSCLC in the second line setting". This comment could be extended to immunotherapies given the suboptimal results shown in recent Phase III studies, as discussed above.

Furthermore, conducting a Phase III RCT in this setting would be difficult given the uncommon frequency of BRAF mutation and the length of time needed to enroll this rare patient population:

- BRAF V600^{+}mutations only occur in approximately 1-2% of patients with NSCLC. The rarity of the patient population precludes access to many patients for a RCT.
- The BRF113928 study, conducted at 69 sites globally, took four years to screen and fully enroll all cohorts (177 patients). A phase III RCT powered to detect overall survival with a HR=0.75 (with alpha=0.05; power=80%) would require 400 patients. Assuming 1.2 patients enrolled/month, such a trial would take 11.6 years to complete.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter would support this initial recommendation proceeding to final pERC recommendation.

____	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.

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
1	pERC Recommendation	Par 2, Line 9	'... OS and PFS benefit in NSCLC patients without a known BRAF mutation status, ...'
3	Summary of pERC deliberation	Par 3, Line 13	'... that have demonstrated OS and PFS benefit in NSCLC patients without a known BRAF mutation status, ...'
4	Summary of pERC deliberation	Par 1, Line 9	'... treatment options reimbursed for NSCLC patients without a known BRAF mutation status'
6	Evidence in brief	Par 3, Line 14	'... OS and PFS benefit in NSCLC patients without a known BRAF mutation status.'
8	Registered clinician input	Par 2, Line 15	'... OS and PFS benefit in NSCLC patients without a known BRAF mutation status.'
9	Patient values on treatment	Par 2, Line 8	'...OS and PFS benefit in randomized trials in NSCLC patients without a known BRAF mutation status.'
11	Adoption Feasibility	Par 2, Line 3	'...OS and PFS benefits in NSCLC patients without a known BRAF mutation status have recently been ...'

2.0 Additional Comments About the Initial Recommendation Document

Page Number	Section Title	Paragraph, Line Number	Additional Comments
1	pERC Recommendation	Par 2, Line 9	Currently, BRAF+ NSCLC patients do not have access to a publicly reimbursed Targeted Therapy for this specific mutation.
3	Summary of pERC Deliberation	Par 3, Line 16	Treating patients without a BRAF mutation does not comply with the approved indication.
6	Evidence in brief	Par 4, Line 3	Same as above
8	Registered clinician input	Par 2, Line 17	Same as above

3.0 References

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.5.2017. National Comprehensive Cancer Network, Inc. 2017.

2. Garon et al. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. N Engl J Med 2015;372:2018-28.

3. Herbst et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016; 387: 1540–50.

4. Fehrenbacher et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016; 387: 1837–46.

5. Reck et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.

6. J Sabari et al. PD-L1 expression and response to immunotherapy in patients with MET Exon 14 altered NSCLC. Presented at the 2017 ASCO Meeting, abstract 8512.

7. Awad et al. Impact of MET inhibitors on survival of patients with MET exon 14 mutant NSCLC. Presented at the 2017 ASCO Meeting, abstract 8511.

8. Clarke et al. Surrogate clinical endpoints to predict overall survival in non-small cell lung cancer trials—are we in a new era? Translational lung cancer research. 2015;4(6):804.

9. Liu et al. Association between time to progression and subsequent survival in ceritinib-treated patients with advanced ALK-positive non-small-cell lung cancer. Current Medical Research and Opinion. 2016:1-8.

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.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 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

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

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 at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on 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. 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.

e) 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.

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 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.

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

i) 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.