pan-Canadian Oncology Drug Review

Registered Clinician Feedback on a pCODR Expert Review Committee Initial Recommendation

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

November 2, 2017

3 Feedback on pERC Initial Recommendation

Name of the drug indication(s):	Dabrafenib and trametinib in combo for NSCLC
Name of registered clinician(s):	Gail Darling
Contact person*:	James Keech

**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 registered clinician(s) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part X Disagree

Please explain why the registered clinician(s) agrees, agrees in part or disagrees with the initial recommendation.

The initial pCODR recommendation concerning the use of dabrafenib and trametinib in advanced non small cell lung cancer (NSCLC) concluded that the committee was not confident about the effectiveness of dabrafenib plus trametinib in previously treated NSCLC patients with tumors harbouring *BRAFV600E* mutations. As a result they recommended against reimbursement of dabrafenib and trametinib in NSCLC. The primary reason for this was the lack of data from randomized trials of this combination, in NSCLC patients with *BRAFV600E* mutations. Specifically the committee felt that extrapolation of data from trials of dabrafenib and trametinib in *BRAF V600* positive melanoma was not appropriate. It also indicated that outcomes from trials in other molecularly defined subsets of NSCLC could not be used to inform decisions about the effectiveness (PFS, OS) of dabrafenib and trametinib.

The Cancer Care Ontario Lung Drug Advisory Committee (DAC) believes this conclusion is does not reflect the large body of evidence available in molecularly defined NSCLC. The table below summarizes evidence from phase II and III 28 trials in molecularly defined subsets of NSCLC, including data presented in the last week at the 2017 ESMO meeting. This includes multiple trials NSCLC with *EGFR* mutations, including *T790M* resistance mutations, *ALK* translocations, *ROS 1* translocations, as well as *BRAF V600E* mutations. Included in this table are data from a second phase II trial of dabrafenib and trametinib as first-line therapy in patients with *BRAF V600E* mutations. These data were presented at the 2017 ESMO meeting last week.

Examining these data it is clear that there is a high correlation in the data observed in single arm phase II trials and subsequent phase III trials comparing molecularly targeted therapies versus chemotherapy. The response rate in phase II trials for afatanib, osimertinib, crizotinib, ceritinib, alectinib and crizotinib in ROS1 positive NSCLC, in almost all these trials exceeds 50%, with PFS data mostly exceeding 6-7 months in previously treated patients and 10 months in untreated patients. The single arm data for combination

therapy with dabrafenib and trametinib in previously treated patients demonstrates an ORR of 63% with PFS of 9.7m. In new data for untreated patients the ORR is 64% and PFS 10.7m.

The Lung DAC recognizes the highest levels of evidence come from high quality randomized trials. pERC believe that a randomized trial of dabrafenib and trametinib is feasible to perform. This trial could not be conducted in Canada and is unlikely to be conducted by cooperative groups without significant support from the pharmaceutical industry. There are no such trials currently registered in clinical trials registries. There are also no plans from Novartis to perform such a trial. Given this information, the Lung DAC believes that decisions need to be made using existing evidence. The large volume of data below provides compelling evidence that high ORR from a targeted therapy in molecularly defined subsets of NSCLC, translates into superior PFS data in comparison to chemotherapy data. The current recommendation will deny Canadian lung cancer patients a highly effective therapy. The argument that other effective treatments exist, does not recognise the high level of activity observed in both trials of dabrafenib and trametinib. In addition, this therapy is not expected to replace immunotherapy, but would be an incremental treatment option. This is the case in all other molecularly defined subsets of NSCLC.

In summary, the Lung DAC would respectfully suggest that the pCODR pERC reassess their decision that there is a lack of effectiveness data. We recognise the limitations of the cost effectiveness data. However, recognition of the effectiveness data would at least allow for potential negotiation around cost.

Trial	Treatment	N	ORR	PFS	OS
EGFR mutations					
IPASS	Carb-Pacl Gef	608 609	47% 71%	6.3m 9.5m HR 0.48	21.9m 21.6m
First Signal	Cis-Gem Gef	150 159	37% 85%	HR 0.61	
NEJ002	Carb-Pacl Gef	115 115	31% 74%	5.4m 10.8m HR 0.30	26.6m 27.7m
WJTOG3405	Carb-Doc Gef	86 86	32% 62%	6.3m 9.2m HR 0.49	39m 36m
Optimal	Carb-Gem Erl	82 83	36% 83%	4.6m 13.1m HR 0.16	
Eurtac	Plat doub Erl	87 86	15% 58%	5.2m 9.7m HR 0.37	19.5m 19.3m
Lux Lung 2	Afatanib (phase II)	129 (70 with EGFR mut)	66%	~12-13m	
Lux Lung 3	Cis-Pem Afat	115 230	23% 56%	6.9m 11.1m HR 0.58	
Lux Lung 6	Cis-Gem Afat	122 242	27% 67%	5.6m 11m HR 0.28	22.2m 22.1m

AURA 1	Osimer phase I/II	201	62%	12.3m	
AURA 2	Osimer phase II	411	66%	11m	
AURA 3	Cis-pem Osimer	140 279	31% 71%	4.4m 10.1m HR 0.34	
ALK					
Profile 1001 (prior treat)	Crizot (phase I)	149	61%	9.7m	
Profile 1005 (prior treat)	Crizot	439	53%	8.5m	
Profile 1007 (second line)	Pem/Doc Crizot	174 173	20% 65%	3.0m 7.7m HR 0.49	immature
Profile 1014	Cis-Pem Crizot	171 172	45% 74%	7.0m 10.9m HR 0.45	47.5m NR
ASCEND 1 (mix of prior treat)	Cerit (phase I)	255	No prior ALK treat 72% Prior ALK treat 56%	No prior treat 18.4m Prior treat 6.9m	
ASCEND 2 (prior ALK treat)	Cerit (phase II)	140	38.6%	5.7m	
ASCEND 5 (prior ALK)	Doc/Pem Cerit	116 115	7% 39%	1.6m 5.4m HR 0.49	
ASCEND 3 (no prior ALK treat)	Cerit (phase II)	124	63.7%	11.1m	
ASCEND 4 (no prior ALK)	Cis-Pem Cerit	187 189	26.7% 72.5%	8.1m 16.6m HR 0.55	
AF001JP (prior treat)	Alec (phase II)	46	Median PFS not reached	PFS 62% at 3 years	
North American trial (prior treat)	Alec	87	52%	8.1m	
Phase III	Criz Alec	151 152	75.5% 82.9%	Not reached at median flup ~18m	12m PFS 68.4% v 48.7%
ALUR ESMO 2017	Pem/Doc Alec	35 72	2.9% 37.5%	1.4m 9.6m HR 0.15	
ROS1					

Shaw (prior treat)	Criz	50	72%	19.2m	
BRAF					
Prior treat	Dabraf + Tramet (phase 2)	59	63.2%	9.7m	
No prior treat ESMO2017	Dabraf + Tramet (phase 2)	36	64%	10.9m	

b) Notwithstanding the feedback provided in part a) above, please indicate if the registered clinician(s) 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.	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

3.2 Comments Related to the Registered Clinician(s) Input

Please provide feedback on any issues not adequately addressed in the initial recommendation based on registered clinician(s) input provided at the outset of the review on outcomes or issues important that were identified in the submitted clinician 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: Are there therapy gaps? Does the drug under review have any disadvantages? Stakeholders may also consider other factors not listed here.

Page Number	Section Title	Paragraph, Line Number	Comments related to initial registered clinician input

3.3 Additional comments about the initial recommendation document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
			pERC should allow non-comparative data for this trial

Clinician Feedback - Dabrafinib and Trametinib

September 2017

Name of the drug indication(s):	Tafinlar-Mekinist combo
Name of registered clinician(s):	Dr. Rosalyn Juergens, oncologist, ON
Contact person*:	Shem Singh & Christina Sit
Title:	Executive Director & Programs Manager

1. Comments on the Initial Recommendation

a) Please indicate if the registered clinician(s) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part _X_ disagree

Please explain why the registered clinician(s) agrees, agrees in part or disagrees with the initial recommendation.

See below.

b) Notwithstanding the feedback provided in part a) above, please indicate if the registered clinician(s) 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.	__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?

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

pCODR pERC Initial Recommendation; Page 3, Paragraph 2 and Sentence 2

pERC Statement:

> and safety of dabrafenib plus trametinib (study BRF113928). 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 trametinib; however, on its own this was not considered to be sufficient evidence of clinical effectiveness. Additionally, investigator-assessed, complete responses were observed in only 4% of patients, with the remainder reporting only partial responses. pERC acknowledged that the current evidence suggests that there is antitumour activity

Response:

We disagree with this assessment. It is noted in the evidence and acknowledged by pERC that there is a response rate of over 60%. We believe that the committee has not given enough consideration to this data point. As stated in the clinician review, the most appropriate historical control is chemotherapy with docetaxel. 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. This represents an incredible response and significant anti-tumour activity.

This response rate of 63.2% is also consistent with that observed for other targeted therapies. In fact, pERC acknowledges on pg. 8 within the initial Clinical Guidance Report (Interpretation) that "In molecularly defined subgroups of NSCLC, including patients with tumours harbouring EGFR mutations and ALK translocations, the likelihood of tumour response to molecularly targeted therapy is almost doubled [of chemotherapy] (60-70%)". The trial results also show that this treatment offers PFS benefits over standard therapy. These points further aligns the efficacy of this targeted therapy with that of others and is also acknowledged in the remarks made by the pERC Clinical Guidance Panel [Pg. 15 Clinical Guidance Report].

pERC notes that only 4% of patients observed a 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]. We believe that the lack of compete response should not be used as an argument against the efficacy of D&T. We remind the committee that in lung cancer, there is a significant unmet need. The 5-year survival rate is only 17%. Complete responses to medication are extremely rare. It is unrealistic to evaluate lung cancer medications using this criteria. Instead, the focus should be on the high response rate.

Initial pCODR pERC Recommendation; Page 6, Paragraph 3, Sentence 1

pERC Statement:

> pERC further considered the feasibility of conducting an 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-center RCT with appropriate comparators would be feasible. pERC

Response:
This statement suggests an overestimation of the size of the BRAF V600 positive patient population. As submitted in LCC's clinician submission, BRAF mutations in lung cancer are extremely rare - BRAF v600E mutations are even rarer. As noted from our 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 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 patients per year with the above information."

Given the rarity of this mutation, the feasibility of completing a RCT in a timely or even reasonable fashion is not possible. As a reminder, this single arm trial of 56 patients took 13 months across 30 centres in 9 countries on 3 continents. 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].

Given the rarity of the mutation, we believe that it is unreasonable, and potentially unethical to conduct a RCT in this population given the strong Phase 2 trial results. pERC must also specifically recognize that there are no ongoing phase 3 trials on these treatments for BRAF V600E positive NSCLC patients. This decision actively discriminates against lung cancer patients with this mutation and all cancer patients with a small numbers as it prevents them from getting an efficacious treatment due to demands for phase 3 trial that will not / cannot / should not be conducted.

Initial Recommendation; Pg. 9, Last paragraph

pERC Statement:

pERC highlighted that that there is a continued need for more effective treatment options for patients; however, given the availability of immunotherapies (nivolumab and pembrolizumab), pERC agreed that patients do have other treatment options. Overall, pERC agreed that dabrafenib plus trametinib partially

Response:
While we agree that immunotherapies are available as an option for these patients, pERC does not have the data to determine that these are better options. In fact, the PAG input states that "PAG the ORR and PFS for docetaxel and Nivolumab in the second line setting are well established and are clearly significantly lower than dabrafenib and trametinib. [Clinical Guidance Report Pg. 9, paragraph 1] The secondary endpoint PFS data with D&T was 10 months. This is the PFS that we see with other approved targeted therapies in lung cancer including first generation EGFR TKI's and crizotinib. This compares favourably to a PFS of 3.9 months with pembrolizumab.

Data and experts agree that lung cancers with oncogenic driver mutations have lower tumour mutation burdens and have lower response rates to immunotherapies. NCCN and ASCO guidelines support the use of a targeted therapy over other options in cases where there is an actionable mutation. Recent ESMO and ASCO data also supports the use of targeted therapies before immunotherapies. In fact, 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 immunotherapies, pERC is supporting a treatment pathway that is contrary to established oncology principles. We express frustration at the assessment that due to the availability of IO, that there is less of a role for D&T. It is recognized that outcomes of NSCLC have improved because we have adopted a personalized or precision approach to treatment. Lumping all patients by saying we have immunotherapy discredits this approach that there may be a subgroup that benefits from a different or personalized approach according to driver mutations and is a step backwards.

pERC Initial Recommendation; Page 8, Paragraph 1

pERC Statements:

1) Registered Clinician Input: Variable Opinion on Comparative Efficacy Against Immunotherapies:

2) Clinical Guidance Report; Page 30, Last Paragraph.

The clinicians in this group input would offer dabrafenib/trametinib as third-line or last line of therapy after platinum doublet and immunotherapy. They viewed dabrafenib/trametinib as a "nice-to-have", rather than a "must-have".

Lung Cancer Canada's Medical Advisory Committee respectfully disagrees with this physician group viewpoint. Our medical advisory committee consists of academic thought leaders from across the country. We believe that as a core oncology principal, a target that shows such efficacious response, is not "a nice to have" option. It is a standard of care.

We disagree with this group's assessment that D&T would be inserted into the treatment algorithm after immunotherapies. PAG also disagrees with this advisory group's assessment. "Based on available data, combination therapy with D&T would insert into the existing NSCLC treatment algorithm following first-line chemotherapy and before immune checkpoint inhibitors such as nivolumab or pembrolizumab. In most patients that would be following platinum-based chemotherapy." [PAG input, Page 10 Clinical Guidance Report]

The initial recommendation suggests that PCODR has taken the advice of this one group in stating that there are other options available. However, while discussion in the scientific community is welcome and common, pERC must recognize that it is generally recognized that patients with an actionable mutation have higher response rates to a targeted therapy. The response that BRAF patients have to immunotherapies is unclear. This is recognized by both our group and PAG. In fact, recent data from ASCO and ESMO also support this principle.

Lung Cancer Canada's Medical Advisory Committee strongly encourages pERC to reconsider this initial recommendation. We recognize that this submission was made on Phase 2 data and that there are limitations. However the response rate shows clear superiority over chemotherapy. It must also recognize that the small number of BRAF v600E patients prohibit a Phase 3 trial from being conducted in a reasonable and timely manner. If pERC does not accept this reality, Canadian BRAF v600 patients may never have access to this life-extending therapy. Finally with the Keytruda decision, pERC has already adopted the approach to use a targeted therapy in patients with an actionable mutation prior to an immunotherapy. As treatments evolve, so must HTA systems. These are not just lines of therapy. Each option is a lifeline for patients. Despite recent advances in lung cancer, there is still a high unmet need and HTA cannot pose a barrier to improved patient outcomes.

1 About Completing This Template

pCODR invites those registered clinicians 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 registered clinician(s) 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 clinician(s), 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.

2 Instructions for Providing Feedback

a) Only registered clinician(s) that provided input at the beginning of the review of the drug can provide feedback on the initial recommendation. If more than one submission is made by the same registered clinician(s), only the first submission will be considered.

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 Clinician 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. Registered clinician(s) 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

registered clinician(s) 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). 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) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca. Information about pCODR may be found at www.cadth.ca/pcodr.

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