PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Ceritinib (Zykadia) for Metastatic Non-Small Cell Lung Cancer

December 3, 2015

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	**Ceritinib (Zykadia™). For the treatment as monotherapy in patients with ALK+ NSCLC, locally advanced or metastatic NSCLC who have progressed on or who were intolerant to crizotinib**
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback:	Novartis Pharmaceuticals

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 ____ agrees in part __x__ disagree

1. pERC has not evaluated all evidence submitted that informs treatment options in patients who progressed while receiving crizotinib therapy (in addition to section: Need, page 5, paragraph 3)

In light of the non-comparative studies (ASCEND-1 and ASCEND-2), and to gain a better understanding of the Canadian ALK+ NSCLC real-world environment, Novartis deemed it important to carry out a retrospective observational study in ALK+ NSCLC patients treated with crizotinib that was provided as part of the June 2015 submission to pCODR. It would appear that the Expert Review Committee (pERC) has not reviewed this evidence as it is not referenced in their initial recommendation. The submitted evidence shows that the majority of ALK+ NSCLC study patients received no further treatment or limited treatment options after discontinuation of crizotinib contrary to what is stated in the initial recommendation with treatment options include *"best supportive care (p1), IV chemotherapy including platinum-doublet (p2), or current standard of care includes pemetrexed, docetaxel and platinum doublet, (p7*)"

The study enrolled 6 centres (2 in BC, 3 in ON and 1 in QC) reporting on 45 patients who progressed while receiving crizotinib therapy. Results of the treatment patterns are reported below (table 1): This study aimed at capturing treatment patterns and outcomes between 2010-2015, the majority of patients received ceritinib (20/45:44%) was unexpected; however, 42% (19/45) of patients received no further treatment, while pemetrexed monotherapy was reported as the next-most utilized agent (10/45:22%). Excluding the use of ceritinib, the majority of patients received no further treatment (Table 1). For the 19 patients who received crizotinib as 1st line agent, 8/19 (42%) patients received no further treatment. (The final data set included 97 ALK+ NSCLC patients; 49 patients were crizotinib-failures, 9 were crizotinib-naïve, and 39 were receiving ongoing treatment with crizotinib at the time of study). No changes in the treatment patterns were noted in the additional 4 crizotinib-failure patients).

These findings remain consistent with treatment patterns reported in the US and Europe, and were included in the submission to pCODR. Of 119 patients with ALK+ NSCLC who discontinued crizotinib in the US, 50 patients (42.0%) who discontinued crizotinib did not receive any additional antineoplastic therapy. Among the remaining 69 patients (58.0%) who did receive antineoplastic therapy, 37 patients (53.6%) received chemotherapy.[1] Based on 85 patients in Europe who discontinued crizotinib, 43.5% (n=37) of patients were reported to have had no further systemic antineoplastic therapy, 29.4% (n=25) received a second-generation ALK inhibitor, 17.6% (n=15) had chemotherapy, and the remaining 9.5% (n=7) of patients received other targeted therapy in combination or crizotinib based regimen and 1 unknown.[2] Final analysis including European dataset, along with the US, Korea and Latin America was presented at ESMO2015. These results were also consistent, with 47% of patients receiving no further antineoplastic therapy, 23% received a 2nd generation ALK inhibitor, 22% treated with chemotherapy.[3]

Table 1: Treatment patterns post discontinuation on crizotinib, by line of treatment (Table 7 of report submitted)[4]

Treatment regimens	Any time post-crizotinib (n=45), n (%)		First-line post-crizotinib, (n=45), n(%)		Second-line post-crizotinib, (n=11), n(%)		Third-line post-crizotinib or later, (n=6), n(%)	
Ceritinib	20	(44.4)	11	(24.4)	6	(54.5)	3	(50.0)
Pemetrexed	10	(22.2)	6	(13.3)	2	(18.2)	2	(33.3)
Carboplatin + Pemetrexed	3	(6.7)	3	(6.7)	0	(0.0)	0	(0.0)
Cisplatin + Pemetrexed	2	(4.4)	2	(4.4)	0	(0.0)	0	(0.0)
Gemcitabine	1	(2.2)	0	(0.0)	0	(0.0)	1	(16.7)
Targeted agent (erlotinib or HSP90 agents)	2	(4.4)	1	(2.2)	1	(9.1)	0	(0.0)
Other Platinum-doublets*	4	(8.9)	4	(8.9)	0	(0.0)	0	(0.0)
Carboplatin + Cisplatin + Gemcitabine	1	(2.2)	1	(2.2)	0	(0.0)	0	(0.0)
No further systemic treatment	19	(42.2)	17	(37.8)	2	(18.2)	0	(0.0)

Other platinum-doublets* include: cisplatin+vinorelbine; carboplatin+paclitaxel; carboplatin+gemcitabine; carboplatin+docetaxel

2. pERC reports "No OS data", section: limitations, page 5, paragraph 2: "*Overall survival data were not reported*".

Median OS data have been reported from both ASCEND-1 and ASCEND-2 studies as well as from retrospective analysis as follows. Please note that comparative OS is rarely reported in clinical trials in oncology, due to crossover. 16.7 months was reported in ASCEND-1 and 14.9 months was reported ASCEND-2 (page 37 of CGP report), with OS rate at 12 months of 67.2% in ASCEND-1 and 63.8% in ASCEND-2. It is to be noted that patients in ASCEND-2 were heavily pre-treated, with the majority receiving more than 3 lines of prior treatment. A sequential retrospective assessment of patients who were treated with crizotinib, followed by ceritinib, reported an OS of 30.3 months.[5] An OS of 20.4 months was reported in the retrospective Canadian study in patients who received ceritinib (anytime) post discontinuation of crizotinib.[4]

In comparison, a median OS of 2 months or 1.7 months was reported in the US and Canadian retrospective study, respectively in patients who received non-ceritinib treatment (combination of systemic treatment and no treatment). If left untreated, patients with ALK+ NSCLC who discontinued crizotinib, had a median survival of 0.6 months and 0.7 months reported in the US and Canadian retrospective study, respectively (Table 2).

Table 2: Summary of OS evidence submitted to pCODR

ALK+ NSCLC previously treated with crizotinib	PFS (% at 12 months)	OS (% at 12 months)	OS (% at 24 months)	Median OS
Ceritinib				
ASCEND-1 (Data cut-off April 12, 2014)	**27.2**	**67.2**	**40.7**	**16.7 months**
ASCEND-2 (Data cut-off August 14, 2014)	**24.5**	**63.8**	**NR**	**14.9 months**
Cumulative retrospective assessment[5]				30.3 months
Canadian retrospective study[4]	-	68.2	37.9	20.4 months
Systemic treatment US Retrospective study[1]	-	-	-	6 months (180 days)
Canadian retrospective study[4]	-	0	0	7.6 months
Best supportive care (All patients) US Retrospective study[1]	-	-	-	2.0 months (61 days)
Canadian retrospective study[4]	-	0	0	1.7 months
No treatment US Retrospective study[1]	-	-	-	0.6 months (17 days)
Canadian retrospective study[4]	-	0	0	0.7 months

3. Phase 3 data availability

As listed in table 3 below, there is an apparent hesitation by the pERC to provide a positive recommendation in light of the availability of future phase 3 data. ASCEND-5 is an event driven study, results of phase 3 may not be available in 1 year. In comparison with a sample of precedent pCODR-evaluated files, which have a similar level of submitted evidence as that of ceritinib, it appears that pERC has provided funding recommendations that have resulted in public payer

listings – table 3.

Table 3: Comparison of previous pCODR recommendations with single arms studies

	Primary endpoint	Net Clinical benefit	Phase 3 availability – randomized study	pERC Recommendation
Xalkori (1st submission)	ORR	Maybe	Yes – within months of 1st submissions	Do not fund
Adcetris	ORR	Maybe	None	Fund with "*condition to collect evidence to reduce uncertainty in cost-effectiveness*"
Erivedge	ORR	Maybe	None	Fund with "*condition to collect evidence to reduce uncertainty in cost-effectiveness*"
Bosulif	ORR	Confident of benefit	None	Fund, with "*condition to collect evidence to reduce uncertainty in clinical benefit and cost-effectiveness*".
Iclusig	ORR	Confident of benefit	None	Fund, with "*collect further evidence to address uncertainty in the magnitude of clinical benefit*"

Please note: other examples not mentioned above is un-intentional.

4. **As adequately recognized by the pERC with regards to the ceritinib submission**
   a. The majority of patients had brain metastases in both studies, yet overall response rate or progression-free survival remain consistent in both patients with brain metastases or without, in line with patient values. The limited efficacy of crizotinib to cross the blood-brain barrier has been documented elsewhere.[6]
   b. The objective response rate was considered promising; The ORR reported with ceritinib were within the range previously reported with crizotinib, despite a patient population with a higher disease burden;
   c. No deterioration in quality of life, as demonstrated in ASCEND-2.
   d. Toxicity with ceritinib is manageable (both ASCEND-1 and ASCEND-2 included up to 300 patients in a post-crizotinib population).

Noting lack of treatment options (section 1), poor survival as a results of limited current treatment options (or lack thereof), and the potential survival benefit with ceritinib (section 2), phase 3 data availability due to being event driven study (section 3), and in light of the positive conclusions noted by pERC (section 4), Novartis proposes the following:

1. **Consider funding ceritinib in patients who have failed antineoplastic therapy and crizotinib;**

While encouraging that the pERC considered a funding recommendation for ceritinib, it appeared that the pERC did not take into account the current funding pathway; i.e. crizotinib is yet to be funded in 1st line across provinces. As such, patients are currently receiving antineoplastic therapy (typically a platinum-doublet) in 1st line and crizotinib in 2nd line. Patients failing crizotinib as adequately recognized by the Clinical guidance panel are currently left with no further option. Hence, it is deemed appropriate to consider funding for ceritinib in patients failing antineoplastic therapy and crizotinib.

2. **Consider a conditional funding recommendation in light of future data being available**

Alternatively, this current submission should make it an obvious possibility to issue a conditional recommendation in light of future robust phase III data availability based on recent recommendations that include further data collection as detailed in table 3. Consideration of this approach would be very much beneficial from a patient perspective (and as duly noted by the PAG, the number of patients affected would be small)

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.

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
5	Limitations	Paragraph 2	No OS Data; The section on limitation of the initial recommendation is misleading. OS data with ceritinib has been reported in page 37 of CGP report. Suggested change: "*mOS data have been reported from both ASCEND-1 and ASCEND-2 studies. Median overall survival of 16.7 months was reported in ASCEND-1 and 14.9 months was reported ASCEND-2 (page 37 of CGP report), with OS rate at 12 months of 67.2% in ASCEND-1 and 63.8% in ASCEND 2.*"

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.

Please note that new evidence will be 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 providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

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.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.

[1] Guerin A, etal. Curr Med Res Opin. 2015 Aug;31(8):1587-97

[2] Analysis Group. Retrospective chart study in ALK+ NSCLC patients who discontinued crizotinib (Europe). Preliminary results. (Data on file). May 2015.

[3] Park K, Cadranel J et al. treatment patterns and survival among crizotinib-treated ALK+ NSCLC: a chart review study. Poster presented at European Society for Medical Oncology (ESMO), September 2015

[4] ICON Epidemiology. Retrospective observational study of patients with ALK+ mutation non-small cell lung cancer treated with crizotinib in Canada. Report prepared for Novartis Pharmaceuticals Canada Inc., May 2015. Data on file.

[5] Gainor J, Tan D, DePas T, et al. Clin Cancer Res; 2015; 21(12): 2745-2752

[6] Awad M, Shaw A. Clin Adv Hematol Oncol 2014;12:429-39.