CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Manufacturer)

Brigatinib (Alunbrig) for Non-Small Cell Lung Cancer

August 1, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Brigatinib (Alunbrig) for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non–small cell lung cancer (NSCLC) who have progressed on or who were intolerant to an ALK inhibitor (crizotinib).
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Group):	Manufacturer
Organization Providing Feedback	Takeda Canada Inc

**The pCODR program 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 eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☐ agrees in part ☒ disagree

Takeda believes that brigatinib's efficacy and safety in the treatment of patients with ALK+ NSCLC in the post-crizotinib setting have been demonstrated in the phase II ALTA trial, phase 1/2 Study 101, and two real-world-studies, with ALTA-1L (first-line, phase III study) providing confirmatory evidence of the robust efficacy and safety. Despite available treatments for ALK+ NSCLC, there is still a need for newer therapies that increase progression free survival (PFS), target brain metastasis effectively and improve overall survival. Brigatinib addresses these unmet needs.

Takeda requests that pERC conditionally recommends reimbursement of brigatinib for the treatment of adult patients with ALK+ locally advanced or metastatic NSCLC who have progressed on or who were intolerant to an ALK inhibitor (crizotinib), until additional clinical data are made available. Takeda commits to providing evidence of the comparative efficacy, including Canadian-specific data (PFS, ORR, QoL) of brigatinib versus alectinib from the results of Study 3001 (phase III comparative trial of brigatinib vs. alectinib in the post-crizotinib setting), and the CARMA/CARMAC study (includes brigatinib in the real-world setting). Results from both studies are expected in late 2021.

Takeda is confident that the results of both studies will be consistent with those already observed in the ALTA and ALTA-1L trials and will provide the certainty that pERC is seeking while still ensuring that patients are able to access the ALK inhibitor with the longest PFS in the target population.

Brigatinib in the 2L post-crizotinib setting is clearly aligned with the unmet medical need identified by physicians, patients and payers. In terms of the pCODR deliberative framework:

- Brigatinib demonstrated Clinical Benefit with an unprecedented systemic PFS of 16.7 months, intracranial PFS of 18.4 months and OS of 34.1 months in the target population in the ALTA trial, which is further supported by the consistency in results observed in the confirmatory ALTA-1L, phase III trial.
- pERC, patients, PAG and physicians noted that brigatinib aligned with Patient-Based Values of having additional treatment options and extending PFS while maintaining QoL, with a tolerable side effect profile and convenient once-daily dosing regimen.
- **Takeda is committed to working with all drug plans to address any Economic concerns while still ensuring that we can increase the treatment options available to patients with ALK+ NSCLC**
- Brigatinib's oral route of administration, convenient once-daily dosing (compared to 8 times/day for alectinib and 5 times/day for ceritinib) and blister packaging is an enabler of Adoption [Feasibility]. PAG specifically noted that oral administration is an enabler to implementation.

b) Please provide editorial feedback on the Initial Recommendation to aid in clarity. 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 No.	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
Page 8	Summary of pERC deliberations	Paragraph 1, line 16	The comparative efficacy and safety estimate obtained may be biased due to these limitations. Takeda indicated that in general, indirect comparison methodology is acknowledged as limited and therefore the data should be viewed with caution. No head-to-head trials exist, thus no conclusive comparative superiority claim is intended.

3.2 Comments Related to Eligible Stakeholder Provided Information

☐ Support conversion to Final Recommendation.

Recommendation does not require reconsideration by pERC.

☒ Do not support conversion to Final Recommendation.

Recommendation should be reconsidered by pERC.

Page No.	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
Page 1	Summary of pERC Deliberations	Paragraph 2, line 5(and throughout) "…not satisfied that there is a net clinical benefit of brigatinib compared with	- Takeda acknowledges that pERC did not recommend to list crizotinib, ceritinib, and alectinib based on phase II data. Upon resubmission with phase III data, approximately 1.5 years later, all three received positive recommendations

Page 3	Summary of pERC Deliberations	alectinib, ceritinib, or single-agent chemotherapy given limitations in the evidence from the available phase II clinical trial" Paragraph 2, line 11 (and throughout) "…pERC was concerned about the strength of the evidence due to inherent biases in non-comparative studies, and reliance on tumour response as the principal measure of benefit."	- The median PFS benefits across studies for ceritinib, and alectinib were consistent between their respective phase II and phase III studies, suggesting that a phase III study using brigatinib in second-line would also yield results similar to those from the phase 1/2 (Study 101) and phase II (ALTA) studies - The confirmatory ALTA-1L ph III trial of crizotinib vs. brigatinib demonstrated a compelling HR of 0.49, confirming the promising efficacy of brigatinib across trials - There is evidence to suggest that the ALK+ NSCLC patient populations enrolled in clinical trials is generalizable to the real-world setting; In two real world studies(RWS) investigating ALK+ NSCLC patient populations, the baseline characteristics, such as age and rates of never-smokers, were very similar to those in the 13 clinical trials enrolling ALK+ NSCLC patients. - Brigatinib's phase III, second-line post-crizotinib study is currently enrolling patients. The study is event-driven and the anticipated completion is August 2021. This timing coincides with interim data availability from the CARMA/CARMAC RWS which will help bring certainty to the results observed in ALTA and Study 3001 in the real-world setting.
Page 4	Summary of pERC deliberations	Paragraph 1, line 7 "…pERC was uncertain whether brigatinib addresses an unmet need."	Per clinician feedback, alternative therapies for second-line treatment following progression on crizotinib provide smaller improvements in PFS than brigatinib: - In accordance with a recent Drug Intelligence report based on a survey of lung cancer treaters across Canada, the percentage of ALK+ NSCLC patients currently on first-line crizotinib in Canada in >60% - Clinical experience using brigatinib post crizotinib showed favorable PFS and toxicity results compared with their institutional experience using ceritinib after crizotinib - In the absence of a head-to-head study, the MAIC analysis compared efficacy of brigatinib with other currently available alk inhibitors and demonstrated numerical improvement for brigatinib versus alectinib and ceritinib, for OS, PFS and ORR, irrespective of whether the pooled ALTA/Study 101 or ALTA data were used.

Page 7	Summary of pERC deliberations	Paragraph 2, line 12 "The reduction in the number of respondents leads to uncertainty in QoL results beyond one year and possibly in earlier cycles."	LCC provided perspective of five patients and four caregivers with experience with brigatinib. - LCC highlighted that brigatinib: (1) was effective in controlling cancer (including brain metastases), (2) had manageable side effects, and (3) allowed patients to have a good QoL. - Patients reported that "brigatinib led to stable disease, reduced or eliminated brain metastases, helped overcome disease resistance to crizotinib, and allowed continuation of an active life style." - The CARMA/CARMAC study and study 3001, will yield data in late 2021 providing QoL data for both brigatinib and alectinib.
Page 11	Adoption Feasibility	Paragraph 3, line 6 "PAG also noted that there may be potential for drug wastage."	- The median dose of brigatinib for patients in Arm B of the ALTA trial was 173.9 mg/day, with the median relative dose intensity in Arm B of 99.5%. Therefore, the potential for dose wastage is minimal. This is also confirmed from Takeda's PSP data that shows most patients are maintained on the 180mg dose.

1 About Stakeholder Feedback

pCODR invites eligible stakeholders to provide feedback and comments on the Initial Recommendation made by the pCODR Expert Review Committee (pERC). (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, pERC makes an Initial Recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The Initial Recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation. It should be noted that the Initial Recommendation may or may not change following a review of the feedback from stakeholders.

pERC welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The Stakeholder Feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the Initial Recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part or disagrees with the Initial Recommendation, and to provide a rational for their response.

   Please note that if a stakeholder agrees, agrees in part or disagrees with the Initial Recommendation, the stakeholder can still support the recommendation proceeding to a Final Recommendation (i.e. early conversion).

2. **Does the stakeholder support the recommendation proceeding to a Final Recommendation ("early conversion")?**

   An efficient review process is one of pCODR's key guiding principles. If all eligible stakeholders support the Initial Recommendation proceeding to a Final Recommendation and that the criteria for early conversion as set out in the *pCODR Procedures* are met, the Final Recommendation will be posted on the CADTH website 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.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), the criteria for early conversion will be deemed to have **not** been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. Please note that if any one of the eligible stakeholders does not support the Initial Recommendation proceeding to a Final pERC Recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the Initial Recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the Initial Recommendation. If the feedback can be addressed editorially this will done by the pCODR staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting.

The Final pERC Recommendation will be made available to the participating federal, provincial and territorial ministries of health and provincial 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) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:

- The Submitter making the pCODR Submission, or the Manufacturer of the drug under review;
- Patient groups who have provided input on the drug submission;
- Registered clinician(s) who have provided input on the drug submission; and
- The Provincial Advisory Group (PAG)

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 *Stakeholder Feedback on pERC Initial Recommendation* can be downloaded from the pCODR section of the CADTH 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 Stakeholder 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.

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 provided to the pERC for their consideration.

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 program.

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

i) If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca

Note: CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback will be posted on the CADTH website (www.cadth.ca/pcodr). The submitted information in the feedback template will be made fully disclosable.