CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Manufacturer)

Osimertinib (Tagrisso) for Non-Small Cell Lung Cancer (first line)

January 4, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Osimertinib (Tagrisso) *First-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations (exon 19 deletions[ex19del] or exon 21[L858R].*
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient: Group, Clinical Group):	Submitter and Manufacturer
Organization Providing Feedback:	AstraZeneca Canada

**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

AstraZeneca Canada agrees with the pCODR expert review committee (pERC) initial recommendation for Tagrisso (osimertinib) in the first-line treatment of EGFRm NSCLC patients and supports early conversion to a final recommendation. AstraZeneca agrees there is a net clinical benefit based on a considerable improvement in progression-free survival (PFS) that was statistically significant and clinically meaningful across all sub-groups of patients. The toxicity profile is manageable despite longer duration with no appreciable decrement in patient's quality of life.

AstraZeneca agrees that Tagrisso (osimertinib) aligns with patient's values of maintaining quality of life, being an effective first-line treatment option and providing an improvement in PFS for patients with central nervous system (CNS) metastases. AstraZeneca agrees that there is a need for options that can offer improved efficacy by extending a patient's progression free survival, circumvent the development of the most common resistance mutation, as well as offer better protection and efficacy for CNS lesions coupled with comparable safety and a well-tolerated adverse event profile. AstraZeneca noted the funding recommendation is specific to exon 19 deletion and exon 21 [L858R] and would encourage the provinces to assess funding of the uncommon mutations on a case by case basis as there is limited clinical evidence for these patients and the data is generalizable.

With respect to the economic analysis, AstraZeneca submitted a 4 health state, semi-Markov model. AstraZeneca believes that the economic evaluation submitted was conservative and in line with a recent peer reviewed publication by Ezeife D and colleagues, that reported an ICER of $223,133/QALY based on a three-health state model evaluating the cost-effectiveness of Tagrisso (osimertinib) in first-line EGFRm patients in Canada(1).

In the submission dossier, substantive evidence, including confirmatory real world evidence, was provided to support a 10 year time horizon for this population (2, 3) and was reflective of the recent pCODR assessment of pembrolizumab in first-line metastatic NSCLC (4) and alectinib in first-line ALK-positive NSCLC (5).

- BC cohort: in patients diagnosed with EGFRm and without CNS metastases, survival was 10% at 10 years, and in those with CNS metastases, survival was <1% at 10 years. A pooled analysis was carried out and provided to pCODR, however, is unpublished. (2)
- US cohort: In patients diagnosed with EGFRm regardless of distant metastases, survival at 9.5 years was ~5%. (3)

Extrapolated PFS curves were aligned to observed data from FLAURA, e.g. time to first subsequent treatment or PFS2 (6) and were selected based on guidance from the NICE TSD report (7). Based on the June 2017 data cut-off, the median time to first subsequent (TFST) with Tagrisso (osimertinib) was 23.5 months. At the time of analysis, the median time to second progression-free survival (PFS2) was not reached. As such, at minimum the submitted economic model was therefore aligned to the median TFST. Based on the pCODR re-analysis, the estimated median PFS2 is 21.7 months which is less than the 23.5 months observed median TSFT data reported from Planchard and colleagues.

The pCODR re-analyses for Tagrisso (osimertinib) in 2L EGFR-T790M patients (May 4, 2017), accepted a Weibull extrapolation for Tagrisso (osimertinib) which was kept consistent in the AstraZeneca 1L Tagrisso economic submission. It is unclear why the extrapolated curve would deviate from the previous assessment of Tagrisso (osimertinib) in this patient population. The curves selected in the 1L pCODR economic re-analysis resulted in patients remaining progression free longer in the 2L setting, which increases the ICER.

Finally, results from a recent assessment of quality of life using EQ-5D questions in patients receiving EGFR TKI at a single-centre (PMH) in Toronto, Canada suggested quality of life is higher despite progression when compared to chemotherapy. highlighting that the model remains conservative if time to treatment discontinuation is considered rather than PFS curves (8)

Many patients with EGFRm NSCLC are often only given one line of therapy and no hope of a cure, in the real-world setting, up to 60% of patients do not proceed to a second line treatment option (2, 9). Given the significant and clinically meaningful benefits over current first-line standard of care demonstrated in the FLAURA trial, AstraZeneca is eager to address feasibility concerns of funding Tagrisso(osimertinib) in the first line setting with the provincial jurisdictions.

AstraZeneca commends and supports the initial recommendation for reimbursement of Tagrisso in first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations. AstraZeneca looks forward to working with pCPA and the jurisdictions in accelerating access to Tagrisso (osimertinib).

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 Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
6	Patient Populations	First Paragraph	Suggest clarifying that the median duration of treatment of 16.2 months for the osimertinib group and 11.5 months for the standard EGFR-TKI group, represents the **treatment duration of exposure**, the definition of which is total dose / total time on drug (ie, days of interruption is excluded). In contrast the time to treatment discontinuation which was defined as the time from randomization to treatment discontinuation or death was 20.8 months for the osimertinib group and 11.5 months for the standard EGFR-TKI group.

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder 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.	☐	Do not support conversion to Final Recommendation. Recommendation should be reconsidered by pERC.

If the eligible stakeholder does not support conversion to a Final Recommendation, please provide feedback on any issues not adequately addressed in the Initial Recommendation based on any information provided by the Stakeholder 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 program.

Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further 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.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information

Reference List

1. Ezeife DA, Kirk V, Chew DS, Nixon NA, Lee R, Le LW, et al. Economic analysis of osimertinib in previously untreated EGFR-mutant advanced non-small cell lung cancer in Canada. Lung Cancer. 2018;125:1-7.
2. Chooback N, Lefresne S, Lau SC, Ho C. CNS Metastases in Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer: Impact on Health Resource Utilization. Journal of oncology practice. 2018;14(10):e612-e20.
3. Lin JJ, Cardarella S, Lydon CA, Dahlberg SE, Jackman DM, Jänne PA, et al. Five-Year Survival in EGFR-Mutant Metastatic Lung Adenocarcinoma Treated with EGFR-TKIs. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2016;11(4):556-65.
4. pCODR. HTA of pembrolizumab in first-line metastatic NSCLC 2017 [Available from: https://www.cadth.ca/sites/default/files/pcodr/pcodr_pembrolizumab_keytruda_nsclc_1stln_fn_egr.pdf.
5. Review p. pCODR assessment of alectinib 1L ALK NSCLC 2018 [Available from: https://www.cadth.ca/alecensaro-non-small-cell-lung-cancer-first-line-details.
6. Planchard D, Boyer M, Lee JS, Dechaphunkul A, Cheema P, Takahashi T, et al. 128O Osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with untreated EGFRm advanced NSCLC: FLAURA post-progression outcomes. Journal of Thoracic Oncology. 2018;13(4):S72-S3.
7. Latimer NR AK. NICE DSU Technical Support Document 16: Adjusting survival

time estimates in the presence of treatment switching. 2014.
8. Shirley Xue Jiang KH, Devalben Patel, Mindy Liang, Catherine Labbe, Frances Shepherd, Natasha Leighl, Penelope Bradbury, Andrew Hope, Catherine Brown, Wei Xu, Geoffrey Liu, Grainne O'Kane. Real-world Health Utility Scores in Patients Treated Beyond Progression with Advanced stage EGFR-mutated Non-Small Cell Lung Cancer ARCC, Canadian Centre for Applied Research in Cancer Control; Montreal2018.
9. Seung SJ HM, Walton R, Evans WK. Real World Treatment Patterns and Survival of Stage IV Non-Small Cell Lung Cancer (NSCLC) in Ontario, Canada. Journal of Thoracic Oncology. 2018.

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.