PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Osimertinib (Tagrisso) for Non-small Cell Lung Cancer

May 4, 2017

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Osimertinib (Tagrisso) for Non-Small Cell Lung Cancer
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	AstraZeneca Canada

**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 Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees __x_ agrees in part ____ disagree

AstraZeneca agrees with and is pleased to receive a positive recommendation from pERC on the net clinical value of Tagrisso, which will address a high unmet need in patients with EGFRm T790M mutation positive NSCLC. Based on AURA 3, Tagrisso demonstrates a statistically significant and clinically meaningful response, PFS and quality of life which is superior to chemotherapy (CGP report, p8).

AstraZeneca also agrees with pERC's assessment that Tagrisso aligns with patient values.

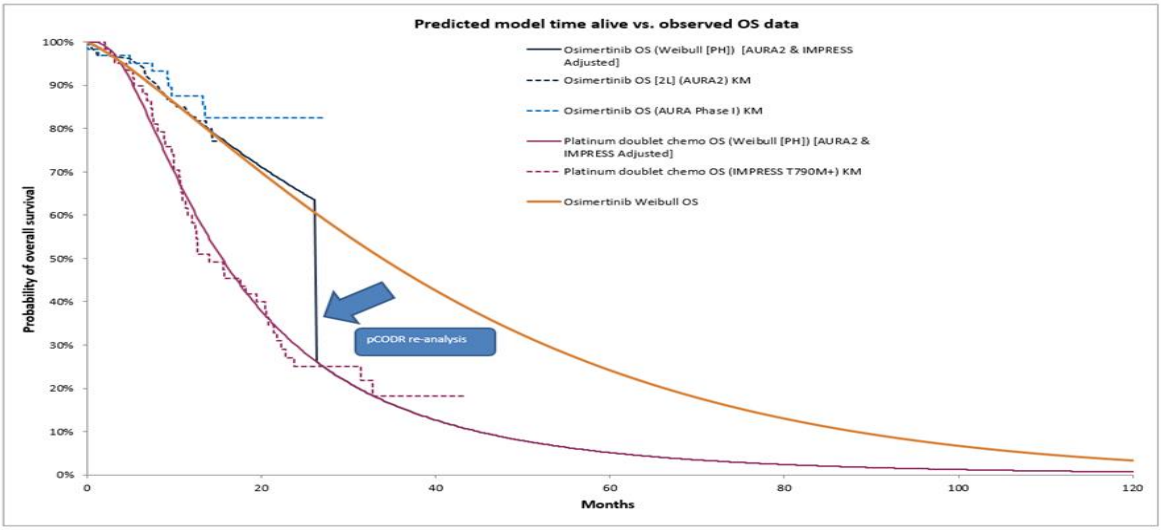
pERC and the EGP raised three issues with the AstraZeneca submitted economic analysis: generic pricing of pemetrexed; model duration; and OS extrapolation. AstraZeneca accepts pERC's and the EGP's comments on the generic pricing of pemetrexed. When the model was submitted, the availability of generic pemetrexed could not be confirmed so the branded price was used. AstraZeneca agrees that the use of the generic price in the model is more appropriate.

AstraZeneca disagrees with the shorter time horizon used by EGP, however, the focus of this response will be on the most clinically implausible component of the reanalysis, the overall survival (OS) extrapolation.

Uncertainty in the magnitude of the OS benefit associated with a new intervention over standard of care (SOC), is a routine concern and dealt with using well-established statistical methods (NICE DSU report on survival analysis, CADTH HE guidelines, 2016). Disagreement on methods employed is always a concern, however, AstraZeneca strongly disagrees with the ICER proposed and clinical plausibility of the approach used by the EGP.

The EGP analysis assumes an "*equal mortality in the post progression state*" (EGP report, p8). As the model is based on a survival-partition analysis, the probability of death from the post-progression state cannot be varied without varying the OS curve. The probability of death (derived by the OS curve) in the model is derived from a combination of patients who

have not progressed on Tagrisso (progression-free state) or progressed and are on subsequent lines of treatment (progression state). As such, the EGP analysis implies that there would be a sudden death from the Tagrisso arm in order to equal the mortality in the chemotherapy arm (as shown in the figure below).



The methods employed by AstraZeneca for the extrapolation of OS are well-established (NICE DSU report on survival analysis). In addition, the justification for the chosen parametric function in the AstraZeneca model was based on literature on the 1L use of EGFR TKIs, which shows an OS expectation in the range of 23-33 months (EURTAC, IPASS, NEJ001, LuxLung3, LuxLung6, LuxLung7). Given that 1L PFS for EGFR TKIs is usually reported in the 10-12 months, it is reasonable to assume that a patient on 2L SOC could expect an OS of around 11-23 months.

The submitted base case analysis estimated the OS benefit for 2L platinum based chemotherapy (SOC) at 17.1 months, which is in the upper half of the survival range and aligns well with the OS data from IMPRESS. Therefore, the submitted model outcome for SOC is supported by the literature.

In the submitted model, AstraZeneca estimated the OS of Tagrisso to be 33.92 months. We believe that the literature on 1L therapy supports this estimate. The body of evidence on the clinical benefits of Tagrisso is consistent with the magnitude of benefit seen with 1L EGFR TKIs. For this reason, it is appropriate to assume that the PFS benefit in 2L would translate to a similar OS benefit in 2L as these patients would follow a similar course to that of a 1L patient. This was part of the rationale for the assumption that the OS for 2L Tagrisso would be in the range of 23-33 months.

Further evidence to support this base case:

1) Longer follow-up of the OS data for Tagrisso can be inferred from the AURA2 study to support the extrapolation;
2) Use of subsequent therapies would provide additional benefit (pERC recommendation, p4, third paragraph) with the utilization of platinum-doublet after Tagrisso, followed by immune checkpoint inhibitor (pERC recommendation, p4, fourth paragraph)

The reanalysis proposed by pERC and the EGP claims that 2/3rd of the survival benefit being accrued beyond progression is unlikely (Initial Recommendation, pg 4). The IMPRESS data,

however, shows the opposite with an OS of just over 16 months and a PFS of 5.3 months demonstrating that at least for the chemotherapy arm a 2/3rd benefit in post progression is the reality for these patients. This is also corroborated by the 1L EGFR TKI literature that shows that a 10-12 month PFS translates to a 23-33 month OS, which demonstrates that 1/2 to 2/3 of the survival benefit occurring post progression is supported by current literature.

Furthermore, an impactful retrospective study from Japan showed that the introduction of Gefitinib to the treatment of EGFR mutation positive NSCLC patients increased OS by 13.6 months. (Takano T et al, 2008). What is noteworthy here is that this is a retrospective study looking at OS before and after the introduction of Gefitinib so there is no cross-over. The original Japanese Gefitinib trials showed an incremental PFS benefit over chemotherapy of 2.9 months and 5.4 months (WJTOG 3405 and NEJ 002) suggesting that there may be a "gearing" effect where the gain in PFS results in a bigger gain in OS. In this case the OS benefit would be 2.5 to 4.7 times the gain seen in PFS. By extension, in AURA3, the incremental PFS gain for Tagrisso is 6.5 months in the BICR assessment. By applying the multiplier above you could reasonably expect a survival gain over chemo of 17 months to 32 months. From this perspective, the estimated 16.85 month median OS gain for Tagrisso over chemo may, in fact, be conservative.

In response to the EGP reanalysis, and to better evaluate the clinical plausibility of the estimated survival curves, AstraZeneca surveyed a group of Canadian lung oncologists who have experience with Tagrisso. They were asked to provide the most clinically plausible OS gain for Tagrisso over platinum based chemo in the the following four ranges:

1. 0-5 months: which is representative of the pERC/EGP reanalysis
2. 6-9 month: OS gain slightly less than the duration of PFS seen for Tagrisso in AURA3
3. 10-12 months: OS gain in the magnitude of PFS seen for Tagrisso in AURA3
4. 12-18 months: OS gain in line with the extrapolated OS curved used in the base case AstraZeneca analysis

The most common response was the range presented in option 4 (an OS gain of 12-18 months) which is in line with the base case submitted by AstraZeneca. The remaining responses were distributed across ranges presented in option 2 and 3.No lung treating oncologist with experience using Tagrisso identified the EGP proposed scenario as clinically plausible.

In conclusion the current re-analysis by the EGP is clinically implausible, deviates from established statistical methods and underestimates the benefits derived from Tagrisso. It ignores the use of subsequent therapies which impact OS. The EGP reanalysis substantially undervalues the positive clinical impact of Tagrisso and AstraZeneca urges pERC to reconsider this component of an otherwise high quality recommendation. In service to this high unmet need and substantial clinical benefit of Tagrisso, it would be prudent for pERC to recognize that in the face of uncertainty around the magnitude of OS benefit attributed to Tagrisso at the very least a range of plausible ICERs should be presented. This plausible range should include AstraZeneca's base case analysis but given the paucity of evidence and justification, should not include the EGP's reanalysis.

References:

Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available from http://www.nicedsu.org.uk

CADTH ECONOMIC GUIDELINES: Draft Guidelines for the Economic Evaluation of Health Technologies: Canada, October 2016

T Takano, T Fukui, Y Ohe , etal: EGFR mutations predict survival benefit from gefitinib in patients with advanced lung adenocarcinoma: A historical comparison of patients treated before and after gefitinib approval in Japan J Clin Oncol 26: 5589– 5595,2008

Mitsudomi T, Morita S, Yatabe Y, et al. Updated overall survival results of WJTOG 3405, a randomized phase III trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer harboring mutations of the epidermal growth factor receptor (EGFR) J Clin Oncol. 2012;30(suppl) abstr 7521

Kobayashi K, Inoue A, Maemondo M, et al (2009) First-line gefitinib versus first-line chemotherapy by carboplatin (CBDCA) plus paclitaxel (TXL) in non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations: a phase III study (002) by North East Japan Gefitinib Study Group. J Clin Oncol 27:Suppl:411s. abstract

Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13:239–246

Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947–957

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Park K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open label, exploratory, randomised controlled trial. Lancet Oncol 2016

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.	__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 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.