CADTH

pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Registered Clinician)

Atezolizumab (Tecentriq) for Small Cell Lung Cancer

Cancer Care Ontario Lung DAC

December 5, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Atezolizumab/SCLC
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Registered Clinician Feedback Cancer Care Ontario Lung DAC

**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 the pCODR program.*

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

The CCO Lung DAC agrees in part with the recommendation. The DAC feels that there is a clinically meaningful benefit; the question is the size and cost-effectiveness. The updated survival data (18 months) demonstrates a survival difference of 13%, which suggests modest clinical benefit and data that is maturing. The economic analysis calculates an ICER of over $400 000 per QALY. The pERC estimate for a cycle of carbo/etoposide cost vs. cis/etoposide cost ignores the difference in administration costs/antiemetics etc. The DAC is unclear why pERC does not change the recommendation to a conditional positive recommendation, noting the modest benefit and need to improve cost-effectiveness, pending negotiation and follow-up data. The possibility of resubmission when the final analysis in 2020 is done will not change the median survival difference, but will give an idea of durability and whether the likelihood of survival at 2 years is higher. The ICER will continue to be a huge issue. The DAC also notes that patients in IMpower133 did not receive consolidative thoracic radiation.

b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

☐ agrees ☐ agrees in part ☐ disagree

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the provisional algorithm. Please note that comments should relate* ***only to the proposed place in therapy of the drug under review*** *in the provisional algorithm. If feedback includes New Information or about other therapies that are included in the provisional algorithm, the information will not be considered and will be redacted from the posted feedback. Substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.*

c) 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 or provisional algorithm) 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 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, including the provisional algorithm, 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

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), including the provisional algorithm. (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, including the provisional algorithm 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), including the provisional algorithm as part of the feasibility of adoption into the health system, 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. If the substantive comments relate specifically to the provisional algorithm, it will be shared with PAG for a reconsideration. 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. Please also note that substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final 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 CADTH staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting. Similarly if the feedback relates specifically to the provisional algorithm and can be addressed editorially, CADTH staff will consult with the PAG chair and PAG members.

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 Sponsor 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) The following stakeholders are eligible to submit Feedback on the provisional algorithm:
   - The Sponsor 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 Board of Directors of the Canadian Provincial Cancer Agencies

c) 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.

d) 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.)

e) 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.

f) 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.

g) 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, and should not contain any language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.

h) 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.

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

j) 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.

CADTH

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

Neratinib (Nerlynx) for Early Breast Cancer

Lung Cancer Canada

December 5, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Atezolizumab (Tecentriq). In combination with a platinum-based chemotherapy and etoposide for the first-line treatment of patients with extensive stage small cell lung
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Organization Providing Feedback	Clinical Group Lung Cancer Canada

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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

When this decision was released, Lung Cancer Canada's Medical Advisory Committee (MAC) and those who were involved in the initial submission were asked for their comments on the decision.

Unanimously the MAC is asking PCODR for reconsideration of the initial negative funding recommendation. The LCC physicians feel it should be a positive recommendation. They strongly disagree with PERC's questions and finding that the mOS of 2 months is not clinically meaningful.

We request reconsideration on the following points.

1) SCLC lung cancer has a high unmet need. It only has a median survival of 7-11 months with treatment.
2) Despite a number of trials, there have been no new treatments for SCLC for decades. This is the first new treatment to be approved by Health Canada.

3) The physicians feel that inadequate consideration has been given to the benefit and endpoints in light of the high unmet need.

a. The benefit observed in IMPOWER 133 with atezolizumab is consistent with recently released trial results of another immunotherapy (durvalumab) /chemo combination for SCLC (the CASPIAN study). IMPOWER 133 demonstrated a mOS of 12.3 on months in the IO/chemo arm vs 10.3 months on chemo alone. Similarly CASPIAN with durvalumab demonstrated a mOS of 13.0 months vs 10.3 months. They are also similar on other measures. The HR for both trials are consistent as IMPOWER 133 has a HR of 0.7 and CASPIAN has a HR of 0.73, and the PFS in IMPOWER 133 is 5.2 months vs 5.1 months in CASPIAN. This consistency increases the certainty of the IMPOWER 133 data. It also emphasizes the difficulty of treating this group and the additional significance of the observed results – thus contradicting PERC's assessment and questions around the clinical significance.

b. The clinicians also believe that PERC has not considered all the data in looking at the clinical significance. As a reminder, the median survival for SCLC in Canada is 7-11 months (Canadian Cancer Statistics 2019). At 1 year, the overall survival rate was 52.7% in the atezolizumab arm versus 38.2% in the chemo only arm and at 18 months, 34% of patients were alive in the atezolizumab arm compared with the 21% in the chemo only arm. The clinicians believe that the HR of 0.7 and the survival benefit at 12 and 18 months carries more weight than the 2 months overall survival benefit. The Hazard Ratio is a clearer reflection of the survival benefit, rather than a single point in time analysis that the median OS represents.

4) The LCC MAC clinicians also reviewed previous PCODR recommendations for immunotherapy submissions and note that other treatments that have had similar HR results have received positive funding recommendations. Therefore with a similar HR to previous positively approved applications, in the context of a clear unmet need, should provide cause for reversal of the initial recommendation. The results are summarized below:

Drug	Disease	Line	Fund?	Year	mOS diff	HR
Ipilimumab	Melanoma	2	Yes	2012	3.6	0.68
Ipilimumab	Melanoma	1	Yes	2015	2.1	0.72
Pembrolizumab	Melanoma	1/2	Yes	2015	NR	0.63-0.69
Nivolumab (vs Ipi)	Melanoma	1/2/3	Yes	2016	NR/NS	0.42/0.93
Nivolumab	NSCLC	2/3	Yes	2016	2.8	0.73
Nivolumab	Renal	2/3	Yes	2016	5.4	0.73

Pembrolizumab (2 doses)	NSCLC	2/3	Yes	2016	1.9/4.2	0.71/0.61
Pembrolizumab	NSCLC (PDL1 50+%)	1	Yes	2017	NR	0.60
Nivolumab	HNSCC	2	Yes	2017	2.43	0.70
Nivo + Ipi (vs either alone)	Melanoma	1	Yes	2017	NR for NI/N	0.55 v Ipi 0.88 NS v N
Pembrolizumab	Urothelial	2	Yes	2018	2.9	0.73
Avelumab	Merkel	2	Yes	2018	12.6 (1 arm)	N/A
Atezolizumab	NSCLC	2/3	Yes	2018	3.8	0.73
Nivo + Ipi	Renal	1	Yes	2018	NR	0.63
Nivolumab	HCC	2	No	2018	15.6 (1 arm)	N/A
Nivolumab	Melanoma	Adj	Yes	2019	RFS	0.65
Durvalumab	NSCLC (stg III)	Cons	Yes	2019	NR	0.68
Pembrolizumab + chemo	NSCLC (nSq)	1	Yes	2019	NR	0.49
Pembrolizumab	Urothelial (CPS 10+)	1	No	2019	18.5 (1 arm)	N/A
Atezolizumab + chemo	SCLC	1	No	2019	2.0	0.70

b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

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Recommendation does not require reconsideration by pERC.

☒ Do not support conversion to Final Recommendation.

Recommendation should be reconsidered by pERC.

Therefore in summary, clinicians ask that PERC reconsider their initial recommendation. The unmet need in SCLC is very high and this is the first new treatment to be approved in decades. The Hazard Ratio of 0.70, and substantial survival benefit at 12 and 18 months demonstrate that atezolizumab in combination with chemotherapy provides clinically meaningful progress in the management of this disease. No other data will be generated for this trial. If PCODR does not reverse their decision, SCLC patients in Canada will not be able to access this treatment. Clinicians ask that PCODR issue a positive funding final recommendation and allow this treatment to proceed to PCPA where a price in line with the observed benefit can be negotiated.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information	
3	2	5	In response to the clinical significance of 2 months	
6	2		Same	

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