CADTH

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

Atezolizumab (Tecentriq) for Small Cell Lung Cancer

December 5, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	TECENTRIQ® (atezolizumab) For the first-line treatment of patients with extensive stage small cell lung cancer (ES-SCLC) in combination with a platinum-based chemotherapy and etoposide. Maintenance TECENTRIQ® should be continued until loss of clinical benefit or unacceptable toxicity
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Group):	Sponsor and Manufacturer
Organization Providing Feedback	Hoffmann-La Roche Limited

**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

Hoffmann-La Roche Ltd. (Roche) disagrees with the pERC initial recommendation as it does not reflect the sentiments and conclusions expressed by the pCODR Clinical Guidance Panel nor the submitted patient and clinician input. After careful review of the pERC initial recommendation and associated guidance panel reports, Roche invites pERC to reconsider several aspects of the submitted evidence:

1. **<u>The IMpower133 OS data is mature and no additional analyses are planned or possible</u>**

- As per the IMpower133 Statistical Analysis Plan Version 3 (dated 14 May 2018), an updated final analysis was planned based on a pre-specified 306 death events. At the updated clinical cut-off date (CCOD) of January 24, 2019, 302 death events had been observed. As a result, the updated CCOD on January 24, 2019 represents the final analysis.
- These final survival outcomes (which were presented at ESMO 2019) were also included in the pCODR submission and review.[1]
- Additional survival follow-up analyses are not possible as study sites have been in clinical closure since Q2 2019. All patients were unblinded over a year ago and there are no longer

any placebo patients enrolled on study. There will be no additional survival results or data available to form the basis of a resubmission for IMpower133 to pCODR.

- The March 24, 2020 date (as stated on clinicaltrials.gov) is the estimated study closing date for safety reporting purposes and is based on the last patient last visit (LPLV) where all the patients have discontinued the study or rolled-over to an extension study.

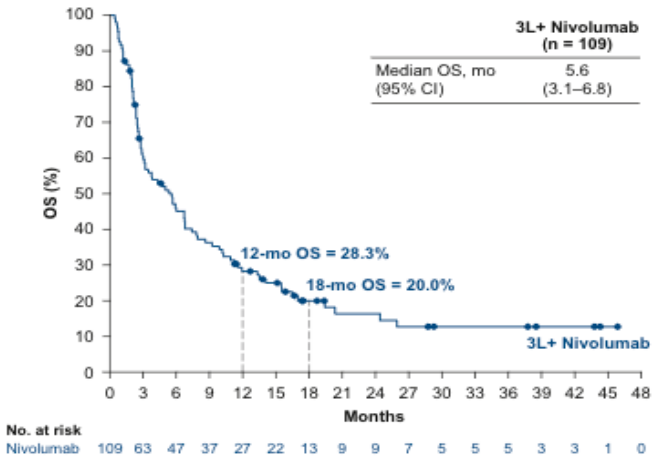
2. <u>The uncertainty in clinical benefit has already been sufficiently addressed through appropriate long-term follow up.</u>

- Given the rapid disease progression and relatively shorter OS rates of patients with SCLC compared to NSCLC (e.g. 5-year relative survival of SCLC is 6.3% vs 23.7% for NSCLC)[2], the median follow-up times of 13.9 months at the clinical cut-off date (CCOD) of April 24, 2018 and 22.9 months at the CCOD of January 24, 2019 are more than sufficient to assess long-term survival.
- In the Institut national d'excellence en santé et services sociaux (INESSS) review, a median follow-up of 13.9 months was noted to be sufficient given the disease in question was ES-SCLC.[3]
- The hazard ratio, difference in median OS, and percentage of patients alive were consistent between the primary and final analysis. Even after 24 months, the survival curves remain separated.

3. <u>Immunotherapies in later lines of SCLC suggest there is a durable and long-term survival benefit in treated patients</u>

- Other ES-SCLC studies have demonstrated a promising flattening of the survival curves (CHECKMATE-032, KEYNOTE-028, KEYNOTE-158, and CHECKMATE-331).[4-7] An illustrative example from CHECKMATE-032 after 28.3 months of follow up is shown in Figure 1. It is reasonable to predict that a similar plateauing of survival curves would be seen in patients treated with atezolizumab + chemotherapy in first-line ES-SCLC.

<u>Figure 1: Overall survival in relapsed SCLC patients (CHECKMATE-032)[8]</u>



Median time from first dose to database lock, 28.3 months. Pooled analysis of third- or later-line nivolumab monotherapy in patients with recurrent SCLC.

4. <u>The magnitude of benefit in IMpower133 is recognized as being clinically meaningful</u>

- IMpower133 was a head-to-head, randomized, double-blinded, placebo-controlled phase III study. This represents the highest standard of evidence in which to evaluate the clinical benefit against the Canadian standard of care.
- While the magnitude of survival benefit may be considered smaller than the benefit observed in NSCLC with the introduction of immunotherapy, it is important to consider that SCLC is an aggressive and fast growing tumour.[9] Over 40 clinical trials in SCLC have failed in the past 20 years thus ES-SCLC patients remain a highly underserved population.[10] Considering that the current standard of care (platinum + etoposide) was adopted in the 1980's largely based on evidence demonstrating comparable efficacy to cyclophosphamide + anthracycline + vincristine (CAV), this suggests that even an incremental survival benefit is significant in this therapeutic space. [11]
- Clinical meaningfulness is further reinforced and validated by:
    - **Regulators**: Priority Review was granted by Health Canada and the FDA - by definition, these designations acknowledge the unmet need in the patient population and signifies that the therapy represents a "...significant improvement in the benefit/risk profile over existing products"[12,13]
    - **INESSS**: The survival benefit was deemed clinically significant and therapeutic value was recognized[3]
    - **Guidelines**: The IMpower133 regimen has been designated a category 1 preferred treatment option for ES-SCLC patients by the National Comprehensive Cancer Network (NCCN)[14]
    - **Canadian Clinicians**: 139 medical oncologists have prescribed atezolizumab + chemotherapy to 166 ES-SCLC patients through the Roche patient support program (as of October 15, 2019)
- Previous positive pERC recommendations have recognized a similar magnitude of benefit as being clinically meaningful in a number of tumour areas (e.g. gastrointestinal hepatocellular carcinoma, advanced melanoma, squamous cell carcinoma of the head and neck etc.) that are similarly difficult to treat with high unmet need.[15-24]

5. The magnitude of clinical benefit needs to be evaluated through a full description of the Kaplan-Meier survival curves

- Median OS represents a single time point, and can easily be influenced by events that occur around that time. The absolute median OS benefit alone does not adequately convey the clinical value of this regimen.
- An assessment of survival benefit requires a description of the median, landmark analyses, and hazard ratio. At the primary analysis of OS[25], the addition of atezolizumab:
    - Increased the median OS by 19.4% relative to carboplatin and etoposide.
    - Reduced the risk of death by a statistically meaningful 30% (HR, 0.70 [95% CI 0.54, 0.91], P=0.0069) over the duration of the trial.
        - The HR is the most appropriate and statistically valid way to evaluate clinical benefit.[26] Visually, the Kaplan-Meier curves in IMpower133 continue to separate past the median.
    - Increased the probability of survival at 12 months to over 50%, an increase of 13% compared to carboplatin and etoposide.

6. Concerns regarding affordability and/or cost effectiveness will be addressed with stakeholders via the existing processes with the pan-Canadian Pharmaceutical Alliance (pCPA)

- Roche is committed to negotiate and ensure these do not act as a barrier for patients to access a safe and effective treatment.

Summary

As part of the pERC deliberative framework, the elements of effectiveness, safety, burden of illness and need are criteria in assessing the clinical benefit of a health technology. These considerations were assessed by the pCODR Clinical Guidance Panel which concluded that "*...there is a net clinical benefit for atezolizumab in combination with platinum and etoposide chemotherapy compared with platinum plus etoposide as first-line therapy for ES SCLC"*. Although the absolute median OS and PFS may be characterized as "modest" at face value (in isolation of the totality of clinical evidence, including landmark survival at 12 and 18 months and HR) the recognition of the great unmet need (no new therapies in the past 20 years), burden of illness (rapidly progressive disease), and the fact that the IMpower133 regimen did not introduce new safety concerns, nor incur a quality of life detriment, establishes that there is a meaningful net clinical benefit for SCLC patients.

Further validation of the clear meaningful clinical benefit of the IMpower133 regimen and the unmet need is evident via the clinician and patient input into pCODR, as well as the fact that priority review was granted by both Health Canada and the FDA, and that INESSS recognized the therapeutic value of the regimen. Additionally, the NCCN practice guidelines have also adopted and recognized the IMpower133 regimen as the preferred therapy for ES-SCLC patients. On the basis of clinical benefit alone – the IMpower133 regimen represents a significant advancement for a disease with overwhelmingly bleak historic outcomes and provides hope for a patient population who have not benefited from new therapies in decades.

Given the final data presented in the submission, along with the feedback from the Clinical Guidance Panel, clinician and patient input, and the urgent need for ES-SCLC patients to access a new safe and efficacious regimen as soon as possible - Roche respectfully requests pERC to reconsider its negative initial recommendation and its potential impact on patients' ability to access a life-extending therapy.

References

1. Reck M, Liu SV, Mansfield AS, et al. IMpower133: updated overall survival (OS) analysis of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide in extensive-stage SCLC (ES-SCLC). ESMO 2019; 2019.

2. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.

3. Institut national d'excellence en santé et services sociaux. TECENTRIQMC – Cancer du poumon à petites cellules. Avis transmis à la ministre en septembre 2019. Available from: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Octobre_2019/Tecentriq_2019_09.pdf

4. Antonia SJ, Lopez-Martine JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016 Jul;17(7):883-895.

5. Ott P, Elez E, Hiret S, al e. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. Journal of Clinical Oncology. 2017;35(34):3823-9.

6. Chung H, Lopez-Martin J, Kao S, al e, editors. Phase 2 Study of pembrolizumab in advanced small-cell lung cancer: KEYNOTE-158. ASCO 2018; 2018.

7. Reck M, Vicente D, Ciuleanu T, et. al. Randomised Phase 3 study of nivolumab monotherapy versus chemotherapy in relapsed small cell lung cancer: Results from CheckMate 331. ESMO-IO2018.

8. Ready N, Farago A, de Braud F, al e. Third-Line Nivolumab monotherapy in recurrent SCLC: CHECKMATE-032. J Thorac Oncol. 2019 Feb;14(2):237-244.

9. Carter BW, Glisson BS, Truong MT, Erasmus JJ.Small cell lung carcinoma: staging, imaging, and treatment considerations. Radiographics. 2014 Oct;34(6):1707-21.

10. Byers LA and Rudin CM. Small cell lung cancer: where do we go from here? Cancer. 2015 Mar 1;121(5):664-72.

11. Chan BA and Coward JIG. Chemotherapy advances in small-cell lung cancer. J Thorac Dis 2013;5(S5):S565-S578.

12. Health Canada. Priority Review of Drug Submissions (Therapeutic Products). Available from: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/prfs_tpfd-eng.pdf

13. U.S. Department of Health and Human Services Food and Drug Administration. Expedited Programs for Serious Conditions – Drugs and Biologics. Available from: https://www.fda.gov/media/86377/download

14. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Small cell lung cancer. Version 2. 2019. Available from: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf

15. Canadian Agency for Drugs and Technologies in Health (CADTH). Abraxane for Metastatic Pancreatic Cancer – Details. Available from: https://www.cadth.ca/abraxane-metastatic-pancreatic-cancer-details

16. Canadian Agency for Drugs and Technologies in Health (CADTH). Yervoy for First Line Advanced Melanoma - Details. Available from: https://www.cadth.ca/yervoy-first-line-advanced-melanoma-details

17. Canadian Agency for Drugs and Technologies in Health (CADTH). Opdivo for Non-Small Cell Lung Cancer – Details. Available from: https://www.cadth.ca/opdivo-non-small-cell-lung-cancer-details

18. Canadian Agency for Drugs and Technologies in Health (CADTH). Zykadia for Non-Small Cell Lung Cancer (Resubmission) – Details. Available from: https://www.cadth.ca/zykadia-non-small-cell-lung-cancer-resubmission-details

19. Canadian Agency for Drugs and Technologies in Health (CADTH). Opdivo for Squamous Cell Carcinoma of the Head and Neck (SCCHN) – Details. Available from: https://www.cadth.ca/opdivo-squamous-cell-carcinoma-head-and-neck-scchn-details

20. Canadian Agency for Drugs and Technologies in Health (CADTH). Onivyde for Metastatic Pancreatic Cancer – Details. Available from: https://www.cadth.ca/onivyde-metastatic-pancreatic-cancer-details

21. Canadian Agency for Drugs and Technologies in Health (CADTH). Keytruda for Metastatic Urothelial Carcinoma – Details. Available from: https://www.cadth.ca/keytruda-metastatic-urothelial-carcinoma-details

22. Canadian Agency for Drugs and Technologies in Health (CADTH). Stivarga for Unresectable Hepatocellular Carcinoma (HCC) – Details. Available from: https://www.cadth.ca/stivarga-unresectable-hepatocellular-carcinoma-hcc-details

23. Canadian Agency for Drugs and Technologies in Health (CADTH). Besponsa for Acute Lymphoblastic Leukemia – Details. Available from: https://www.cadth.ca/besponsa-acute-lymphoblastic-leukemia-details

24. Canadian Agency for Drugs and Technologies in Health (CADTH). Lenvima for Hepatocellular Carcinoma – Details. Available from: https://www.cadth.ca/lenvima-hepatocellular-carcinoma-details

25. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer.N Engl J Med. 2018 Dec 6;379(23):2220-2229.

26. Rich JT, Neely JG, Paniello RCA practical guide to understanding Kaplan-Meier curves.Otolaryngol Head Neck Surg. 2010 Sep;143(3):331-6.

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

☐ agrees ☐ agrees in part ☐ disagree

Not applicable (The pre-submission information form for this submission was sent to pCODR before July 1, 2019)

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.