pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Manufacturer)

Durvalumab (Imfinzi) for Non-Small Cell Lung Cancer

May 3, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Durvalumab (Imfinzi®) *For the treatment of patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy*
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 (AZC) supports the recommendation to reimburse Imfinzi (durvalumab) in stage III NSCLC based on the significant net clinical benefit, manageable toxicity profile and no detriment to quality of life (QoL). AstraZeneca commends pERC's recognition of the "significant need for effective treatment that will delay progression and prolong survival" for patients with Stage III non-small cell lung cancer (NSCLC) "as there are no curative intent treatment options after concurrent chemoradiation therapy, which is associated with a poor prognosis".

AstraZeneca agrees that durvalumab aligns with patient's values as "an effective treatment option that delays disease progression and prolongs survival and has manageable toxicities with no observed detriment to QoL". As noted by pERC, the clinical guidance panel, and all stakeholder input, there have been no advancements in treatment options for these patients in over two decades and there remains an unmet need in this stage where the treatment intent is curative.

Exclusion of Patients Receiving Sequential CRT

AZC respectfully recommends that pERC consider enabling clinicians to make case-by-case determinations as to whether a patient who received *curative-intent* sequential chemoradiation therapy (CRT) could benefit from durvalumab by revising their recommendation to "treatment of patients with locally advanced, unresectable stage Ill NSCLC following *curative intent* platinum-based CRT". While the PACIFIC study required patients to have received at least two or more overlapping cycles of chemotherapy with definitive radiation therapy, the pERC recommendation criteria is more restrictive than both the recommendation from Institut national d'excellence en santé et en service sociaux (INESSS) and the Health Canada-approved indication of "treatment of patients with locally

advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy."[1] There is a significant unmet need for patients in this setting where the standard of care following CRT is "watch and wait", and the pERC recommendation could result in implementation challenges and inequity of patient care across Canada.

A retrospective study in Alberta examining the use of radiation therapy in patients with Stage III NSCLC found that patients in the community and rural settings had lower rates of radiation therapy, possibly linked to geographic and other barriers to the academic centres with capacity for radiation therapy.[12] These barriers identified for patients receiving treatment in community and rural settings could also contribute to patients receiving sequential CRT. As noted in the CGP, two of the four clinician inputs supported the inclusion of patients who received sequential CRT, as they could benefit from treatment with durvalumab within six weeks of their last dose. This clinician input noted that the most common reason for patients receiving sequential CRT is the "absence of a radiation facility at the institution where the patient is receiving chemotherapy". Additionally, the clinicians consulted by INESSS noted that patients who are not able to receive concurrent CRT could plausibly benefit from durvalumab, as there is nothing that suggests the efficacy would be different if administered after sequential CRT.[13]

The treatment goal for patients with unresectable Stage III NSCLC is curative intent through eliminating intrathoracic disease, preventing local recurrence, and reducing the incidence of distant metastases.[2,3] Radiotherapy is given to achieve local control, while the aim of systemic chemotherapy is to prevent the development of distant metastasis. When systemic chemotherapy is added during the course of radiotherapy, it also acts as a radio-sensitizing agent to increase the therapeutic index of radiation therapy.[4,5]

While treatment guidelines generally recommend concurrent CRT for patients with unresectable Stage III NSCLC, sequential CRT is used in some instances.[6] The consensus paper generated at the second ESMO Consensus Conference on Lung Cancer notes that treatment with induction chemotherapy and high-dose radiotherapy (60–66 Gy cumulative) can be given with curative intent for patients who are not considered to be fit for concurrent CRT.[7] In Canada, in the provincial treatment guidelines for this patient population in Alberta, British Columbia, Ontario, and Saskatchewan, the current standard of care involves CRT administered either concurrently or sequentially.[8,9,10,11]

AZC therefore recommends that pERC consider revising their recommendation to "treatment of patients with locally advanced, unresectable stage Ill NSCLC following curative intent platinum-based CRT" to enable clinicians to determine on a case-by-case basis whether a patient receiving curative-intent sequential CRT could benefit from durvalumab. This scenario is not dissimilar to the pERC recommendation on the time to treatment initiation following CRT. Both of these examples allow for generalizability outside of the trial with the goal to ensure there is equity of care for patients across Canada and that patients are treated based on their clinical presentation and not negatively impacted by challenges with implementation that are driven by access to resources.

No Further Treatment Benefit After 3 Years

AstraZeneca recognizes the concerns of the CGP/EGP regarding the assumption of treatment waning and the cost of administration.

Understandably, there is no definition of "cancer clinic" provided in literature.[14] However, based on the study carried out with Ontario-ICES,[15] we have been informed that the cost of

administration, chair time, infusion, supply costs, etc…are captured under the cost of "cancer clinic".

More importantly, we hope to address the concerns regarding treatment waning (defined as no additional treatment benefit from durvalumab as of 3 years);

Based on the recent EMA request, OS data with a longer follow-up is available (providing OS follow-up for additional 12 months), thereby further confirming that benefit extends beyond 3 years. AstraZeneca is keen to share the latest OS update (DCO3, March 2019) with the pCPA.

Nonetheless, based on the submitted evidence, we believe the 3-year waning assumption underestimates the benefits of durvalumab for the following reasons;

1. At the time of DCO2 (March 2018), based on the median follow-up of 25.9 months (lower range: 16.4, upper range: 40.5 months), patients who received durvalumab had a lower risk of progression or death than the placebo arm during the entire follow-up period, despite discontinuation after a treatment period of 12 months.
2. At the time of DCO2, 48.9% of patients who received durvalumab were censored compared to 27% in the placebo arm.[16] Based on the PFS Kaplan-Meier curves, at year 3, 20.8% more patients in the durvalumab arm were progression-free and alive compared to the placebo arm (37.6% vs 16.9%).[16] A treatment waning at 3 years would suggest that the sustained treatment benefit would abruptly stop.
3. Based on DCO2, the time to distant metastasis was longer with durvalumab compared to the placebo arm (median of 28.3 vs. 16.2 months).[16] The frequency of new lesions, as assessed by blinded independent central review, was lower in the durvalumab arm compared to the placebo arm (22.5% vs. 33.8%), with a lower incidence of new brain metastases in the durvalumab group than in the placebo group (6.3% vs. 11.8%).[16]
4. The submitted estimate was still conservative and reflective of payer concerns, as a treatment waning was applied at 10 years. In the metastatic setting, long-term survival tails have been reported with immunotherapies [17,18]. We believe patients in the stage III setting treated with curative intent, have greater chance for long term sustained benefit.

It is therefore likely that there would be sustained survival benefit after 3 years in patients treated with curative intent with durvalumab. As recognized by the pERC that durvalumab is potentially curative and could likely offset subsequent downstream cost, by assuming no further benefit after 3 years substantially underestimates the benefit and artificially increases the ICER. Finally, we hope to address the comment by the EGP; "*if there is an incremental benefit in overall survival extending beyond 3 years, then the incremental QALYs would likely increase to those observed in the submitted base case*", with the updated OS data (DCO3, March 2019).

The magnitude of PFS and OS benefit reported in patients treated with durvalumab was sustained and unprecedented, where currently, the majority of patients treated with CRT only progress within 1 year of treatment, as duly recognized by the pERC. Updated follow-up OS data, confirms that benefits extends beyond 3 years, as such AstraZeneca maintains that the submitted base case remains the most appropriate analysis evaluating the cost-effectiveness of durvalumab.

There is a significant and clear unmet medical need for an effective treatment strategy for patients with Stage III unresectable NSCLC that increases the chances of cure and delays progression to Stage IV metastatic disease. Importantly, patients have little chance of cure once they progress from Stage III to Stage IV metastatic. Given the significant and clinically

meaningful benefits over watch and wait demonstrated in the PACIFIC trial, AstraZeneca is eager to address feasibility concerns of funding durvalumab in the Stage III NSCLC setting with the provincial jurisdictions. Of note, the budget impact models were aligned to the requested funding criteria including the patients treated with curative intent sequential CRT.

In conclusion, AstraZeneca commends and supports the initial recommendation for reimbursement of durvalumab for Stage III NSCLC, though respectfully encourages pERC to reconsider and include patients receiving curative intent sequential CRT on a case by case basis, and to agree that treatment benefit with durvalumab sustains and extends beyond three years. AstraZeneca looks forward to working with pCODR, pCPA, and the jurisdictions in accelerating patient access to Imfinzi (durvalumab).

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

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
1	pERC Recommendation	Paragraph 1, line 3	Restriction to “concurrent only”
4	Summary of pERC Deliberations	Paragraph 2, line 11	Relative treatment effect for OS for durvalumab and observation to be the same at three years

Reference List

1. IMFINZI® (durvalumab) Product Monograph dated January 28, 2019: https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/Imfinzi-product-monograph-en.pdf
2. Eberhardt WE, De Ruysscher D, Weder W, Le Pechoux C, De Leyn P et al. (2015) 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol 26 (8): 1573-1588.
3. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA et al. (2017) Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 28 (suppl_4): iv1-iv21.
4. O'Rourke N, Roque IFM, Farre Bernado N, Macbeth F (2010) Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev (6): CD002140.
5. Ramnath N, Dilling TJ, Harris LJ, Kim AW, Michaud GC et al. (2013) Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143 (5 Suppl): e314S-e340S.
6. Rodrigues G (2016) Cons: concurrent chemo-radiotherapy remains the ideal treatment in fit patients with inoperable large volume stage III non-small cell lung cancer. Transl Lung Cancer Res 5 (2): 195-197.
7. Eberhardt WE, De Ruysscher D, Weder W, Le Pechoux C, De Leyn P, Hoffmann H, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol. 2015;26(8):1573-88.
8. Alberta Health Services (2012) Non-small cell lung cancer stage III.
9. British Columbia Cancer (2014) Non-small cell lung cancer (NSCLC). Available at: http://www.bccancer.bc.ca/books/lung/management/non-small-cell-lung-cancer-nsclc.
10. Cancer Care Ontario (2017) Treatment of patients with stage III (N2 or N3) non-small cell lung cancer. Available at: https://www.cancercareontario.ca/en/content/treatment-patients-stage-iii-n2-orn3-non-small-cell-lung-cancer.
11. Saskatchewan Cancer Agency (2015) Provincial non-small cell lung cancer treatment guidelines. Available at: http://www.saskcancer.ca/Non%20Small%20Cell%20Lung%20CPGs%2004-2015.
12. Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. Sep 2016;27(suppl 5):v1-v27.
13. IMFINZI[MC] – Cancer du poumon non à petites cellules. Avis transmis à la ministre en février 2019. Available at:

https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Mars_2019/Imfinzi_2019_02.pdf
14. de Oliveira C, Weir S, Rangrej J, Krahn MD, Mittmann N, Hoch JS, Chan KKW, Peacock S. The economic burden of cancer care in Canada: a population-based cost study. CMAJ Open. 2018 Jan 4;6(1):E1-E10.
15. Seung, S.J., Hurry, M., Hassan, S., Walton, R. & Evans, W.. Costs and Resources of Advanced Non-Small Cell Lung Cancer Using Administrative Data. Current Oncology (April 2019).
16. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. The New England journal of medicine. 2018;379(24):2342-50.
17. Gettinger S, Horn L, Jackman D, Spigel D, Antonia S, Hellmann M, et al. Five-Year Follow-Up of Nivolumab in Previously Treated Advanced Non-Small-Cell Lung Cancer: Results From the CA209-003 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(17):1675-84.
18. Herbst RS, Dubos Arvis C, Ahn M-J, Majem M, Fidler MJ, Surmont V, et al. Use of archival versus newly collected tumor samples for assessing PD-L1 expression and overall survival: an updated analysis of KEYNOTE-010 trial. Annals of Oncology. 2019;30(2):281-9.

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.