

PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types

General/overall comments

Please note, comments that are beyond the scope of PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types will not be considered

Thank you for the opportunity to provide input into this consultation. Please see our responses to the specific questions over the next pages.

CADTH is transitioning from a Health Technology Assessment agency to a Health Technology Management enterprise. For more details, please

visit: https://www.cadth.ca/sites/default/files/corporate/planning_documents/CADTH_2018-2021_Strategic_Plan.pdf

To that end, several questions asked in this consultation touch on key priorities that we have set out for ourselves over the next three years. These are all challenging questions with no easy answers. In response, we share with you our experiences to date on some of the issues raised, particularly through our pan-Canadian Oncology Drug Review (pCODR) program.

We welcome the opportunity to discuss further and exchange learnings.

Specific responses

Please insert your comments against the consultation questions below.

Question 1

What do you/your organisation see as the potential advantages of the PBAC considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings?

CADTH has not reviewed PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings, though we think some potential advantages to this approach may include:

- Facilitating earlier access to treatments for sub-populations of patients who might otherwise have no/limited treatment options available to them. However, while earlier access may be considered a desirable outcome, it should be acknowledged that it may come at the expense of introducing drugs with limited evidence of efficacy or effectiveness which could introduce considerable patient risk and unnecessary cost to the health care system.
- Creating opportunities to set up innovative pricing arrangements.

Question 2

What do you/your organisation see as the potential disadvantages of the PBAC considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings?

CADTH has not reviewed PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings, though we think some potential disadvantages to this approach may include:

- Facilitating access to treatments that may be ineffective and/or harmful for sub-populations of patients, i.e. patients with cancer types with no/limited data and to whom data are being extrapolated.
- Facilitating access to treatments that may not be cost-effective for sub-populations of patients, i.e. patients with cancer types with no/limited data and to whom data are being extrapolated.
- Increasing financial burden (budget impact) for payers because of the increase in market size to include coverage for indications which may have more uncertainty clinical effectiveness.
- Viability of implementation, e.g., creating processes, if not already in place, to conduct reassessment of treatments for sub-populations of patients, i.e. patients with cancer types with no/limited data and to whom data are being extrapolated.

Question 3

What is urgent unmet clinical need? How should it be established? For which patient groups?

Through the Common Drug Review (CDR) and pCODR processes, CADTH engages several stakeholders to understand and identify unmet clinical need, chiefly patients and clinicians.

Patients complete a standard template that asks them, among other aspects, of their experiences with currently available treatments. The template can be found here: <https://cadth.ca/sites/default/files/cdr/cdr-pdf/CADTH-patient-input-template.docx>. Information collected on this template provides insights into how well a drug under review might address gaps if current therapies fall short for patients and caregivers.

Clinicians can also comment on the relevance of a drug under review to clinical practice, giving them an opportunity to explain how important it would be to have the drug, whether there is an unmet need, and how and when they

would use the drug.

Question 4

What is the minimum level of evidence of effectiveness that you/your organisation think should be required before a PD-1 and PD-L1 checkpoint inhibitors is considered for subsidy for a particular kind of cancer? Why?

At CADTH, through the pCODR program, pERC has reviewed PD-1 and PD-L1 checkpoint inhibitors (issuing 11 final recommendations) without setting a minimum level of evidence of effectiveness. Recent examples include:

- Pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy (<https://www.cadth.ca/keytruda-metastatic-urothelial-carcinoma-details>)
- Nivolumab for the treatment of adult patients with classical Hodgkin Lymphoma (cHL) that has relapsed or progressed after autologous stem cell transplantation (ASCT) and brentuximab vedotin (<https://www.cadth.ca/opdivo-classical-hodgkin-lymphoma-after-failure-asct-details>)

In both reviews, our literature search sought to identify published or unpublished randomized controlled trials (RCTs). In the absence of RCT data, we sought fully published clinical trials that investigated the efficacy and safety of the drug under review. Of note, both drugs received a conditional reimbursement recommendation (the condition being that cost-effectiveness should be improved to an acceptable level) from the pCODR Expert Review Committee (pERC), despite the committee seeing different levels of evidence in each review: in the pembrolizumab review, the committee deliberated on a phase III, multi-centre, open-label RCT; while in the nivolumab review, there were two single-arm, non-randomized studies, of which one was phase I and the other was phase II. In each case, the committee was satisfied that there was a net clinical benefit of the drug under review. Of note, in deliberating nivolumab, pERC noted “a substantial need for treatment options.”

Question 5

Do you/your organisation think it is possible for the PBAC to be able extrapolate, or apply, the evidence of effectiveness of a checkpoint inhibitor in one kind of cancer to another kind of cancer, or from late stage cancer to early stage cancer? Why? How?

CADTH has not had experience in extrapolating the evidence of effectiveness of a checkpoint inhibitor in one kind of cancer to another kind of cancer, or from late stage cancer to early stage cancer. It is not part of the current standard approach for the CADTH drugs reviews.

Question 6

Do you/your organisation think it is possible for PBAC to satisfy itself that treatment with a PD-1 or PD-L1 checkpoint inhibitor is cost-effective without an economic model that is specific to that kind of cancer? How?

- Is it possible to group different cancer types together based on particular characteristics that are similar, and construct a single model for the group?
- Are other approaches to establishing cost-effectiveness across cancer types possible? What are those approaches and how would they operate?

CADTH has developed economic guidelines to help standardize and facilitate the economic evaluation of health technologies in Canada. The 4th Edition of these guidelines were published in March 2017 and are available here: https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf

The guidelines emphasize the need to have a “Decision Problem,” which frames the study question of an economic evaluation in a way that directly addresses the decision problem, or policy question. This includes the target

population(s) for the treatment and its expected use. Within the target population, the value of a treatment will often differ among subgroups. Whether and how the value of the treatment varies by subgroup may be of interest to the decision-maker. Where this is relevant, a decision problem should be specified for each subgroup. This will ensure that any differences in the other components of the decision problem are appropriately captured, or confirm the assumption that all other factors in the decision problem are unaffected.

Question 7

What do you/your organisation think is a reasonable subsidy price for Government to pay for a PD-1 or PD-L1 medicines for cancer types where the benefit is potentially very modest?

It is beyond CADTH's mandate to set prices for treatments.

Question 8

Do you/your organisation think PD-1 and PD-L1 medicines should be made available to all patients whose cancers display a particular biomarker? Why? Which biomarker?

At CADTH, through the pCODR program, as an example, we reviewed two drugs (pembrolizumab and nivolumab) for the same cancer type (non-small cell lung cancer) and while both received a conditional reimbursement recommendation, one (pembrolizumab) was for patients whose cancers displayed a particular biomarker (PD-L1 $\geq 1\%$) while the other (nivolumab) was not. In both cases, pERC's recommendation was consistent with the respective Health Canada indication; the respective manufacturer's funding request; and, the design of the included trials. Perhaps most relevant to this question is the following note that pERC included in its recommendation for nivolumab:

Given the considerable uncertainty that exists concerning the role of PD-L1 testing and whether there is a threshold level below which patients should not be treated, pERC agreed that nivolumab should be made available to patients irrespective of PD-L1 levels. Therefore, testing for PD-L1 will not be required.

The final recommendation for pembrolizumab can be found here: https://cadth.ca/sites/default/files/pcodr/pcodr_pembrolizumab_keytruda_nsclc_fn_cgr.pdf. The final recommendation for nivolumab can be found here: https://cadth.ca/sites/default/files/pcodr/nivolumab_opdivo_nsclc_fn_rec.pdf

Question 9

Do you/your organisation think it is appropriate for the PBAC to extrapolate the evidence from one PD-1 or PD-L1 checkpoint inhibitor to other medicines in the same class(es). This could provide patients with more choice and give Government the opportunity to negotiate better subsidy prices by utilising the competition between sponsors of medicines.

CADTH has not had experience in extrapolating the evidence from one PD-1 or PD-L1 checkpoint inhibitor to other medicines in the same class(es). It is not part of the current standard approach for the CADTH drugs reviews.

Question 10

Do you/your organisation think that different evidentiary requirements are appropriate for rare cancers? How do you think cost-effectiveness should be established in this case?

CADTH does not have different evidentiary requirements for rare cancers, nor are there any special considerations for rare cancers in the aforementioned economic guidelines.

Question 11

Do you/your organisation think PBAC should set aside one of its meetings each year to consider only PD-1 or PD-L1 inhibitors for cancer? (This would mean no other submissions for other medicines, including other cancer medicines, or other diseases would be considered at that meeting.)

At CADTH, the pCODR program has an established performance target of 180 calendar days from the date of a submission being accepted for review to the date of issuing the Initial pERC recommendation. As a result, no pERC meetings are set aside to only consider PD-1 or PD-L1 inhibitors for cancer. Per the *pCODR Procedures* (<https://www.cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pcodr-procedures.pdf>), all drugs under review are given placement on the target pERC meeting agenda pursuant to the following order:

- Any Submission undergoing a procedural review
- Any Submission meeting priority review criteria
- Any Resubmission meeting priority review criteria
- Submissions for New Oncology Drug Submissions or Oncology Drugs with a New Indication
- A Request for Advice
- Reconsiderations of an Initial Recommendation
- Resubmissions

Question 12

If limited evidence is available at the time of subsidy of a PD-1 or PD-L1 inhibitor for a type of cancer, what do you/your organisation think should happen afterwards?

- Should sponsors be required to collect more evidence?
- What should happen if the new evidence shows the medicine is less effective or has greater safety risks than expected?
- Should the medicine continue to be subsidised but at a price commensurate with its benefit? Should the sponsor be compelled to continue to make the medicine available even if it thinks the price is too low?

Adopting a life-cycle approach to health technology assessment is one of three strategic goals and objectives that CADTH has set out in its 2018-2021 Strategic Plan, as mentioned in the general comments. As part of this plan, CADTH is looking to implement programs for reassessment and disinvestment, and these are some of the many questions through which we are working.

Question 13

(For industry/clinical groups) Clinical study information: (Please use the template provided for this information.)

- In what indications has your organisation completed clinical trials with a PD-1 and PDL1 inhibitor? Please include both positive and negative studies.
- In what indications is your organisation currently conducting or planning to conduct clinical trials with PD-1 or PD-L1 inhibitors? If usual PBAC processes were to be followed, when would you expect to make an application for subsidy for these indications?
- How does your organisation decide which indications to study and which to prioritise for registration or subsidy?

Not applicable.

Question 14

Are there effective international models for multi-tumour subsidy that could be applied in Australia within the current regulatory framework?

CADTH is not aware of effective international models for multi-tumour subsidy that could be applied in Australia within the current regulatory framework.

Question 15

(For Industry) What information can you provide regarding established international agreements for multi-tumour subsidy and how could these apply in the Australian regulatory context?

Not applicable.

Question 16

Is there anything else you/your organisation would like to add?

No, thank you again for the opportunity to provide input.