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

We thank the PBAC for the opportunity and we are delighted to see recommendations sought from various stakeholders.

The FDA approval of PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings in an important step in precision medicine and cancer management. However, this development is introducing several challenges to healthcare systems pertaining to the best way to assess value for money and subsidise these therapies. We believe that creative and non-traditional approaches should be followed to strike the balance between early approval/access to immunotherapies and evidentiary requirements. This requires more acceptance of real-word and fit for purpose evidence, innovative economic modelling approaches, and flexible risk-sharing arrangements (e.g. Managed Access Program). Importantly, any evaluation framework should be patient-centred, transparent, guided by rigorous analytical methods, and responsive to the needs of stakeholders (e.g., maximising health system benefits and rewarding innovation).

We provide general recommendations of how we believe this could be appropriately and practically achieved. We would be very delighted to work with the PBAC and other stakeholders to support this initiative.

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?

The recent FDA approval of cancer treatments based solely on the presence of a genetic feature in a tumour, rather than cancer type, is an important step in precision medicine and cancer management. Although patients with certain cancer types, like lung cancer and melanoma, typically have good responses to immune checkpoint inhibitors (e.g. pembrolizumab), not every patient with one of these cancer types responds well to the treatment. For example, patients with tumours that have more DNA mutations, like microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours, are most likely to respond. Thus, patients should be stratified into specific groups via predictive biomarkers that can identify patients with a greater chance of responding to a therapy. Thus, it is important for the PBAC to consider the value for money of the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings. Multi-tumour listings of PD-1 and PD-L1 checkpoint inhibitors may enhance and expand patient access to these medicines particularly for patients with rare cancers.

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?

There is no disadvantage in considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings; however, there are challenges in terms of the best approach to evaluate these drugs and handling uncertainty pertaining to the available evidence on safety, effectiveness, cost-effectiveness and budget impact. Furthermore, despite the promising anticancer activity offered by PD1 and PD-L1 inhibitors, predicting tumour responses to PD-1 and PD-L1 checkpoint inhibitors using appropriate predictive biomarkers remains a challenge.

Question 3

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

These agents have demonstrated promising response rates and durations in diseases such as MSI-H or dMMR endometrial cancer, biliary cancer, or pancreatic cancer, with 40% tumours had measurable tumours shrinkage after treatment, and for 78% of these responders, their tumours shrank or stayed the same size for 6 or more months. Unmet clinical need should remain targeted to the patient groups where there is evidence of effectiveness and value for money.

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?

The gold standard is to have evidence about hard outcomes (e.g. overall survival) from randomised-controlled trials; however, randomised trials to assess overall survival in rare tumour types may not be feasible and/or ethical. There are also challenges to conducting randomised trials on the PD-1 and PD-L1 checkpoint inhibitors such as the difficulty in designing clinical trials due to limited understanding of the natural history and epidemiology of the rare tumours included, absence of standard companion diagnostic tests, limited number of participants, population heterogeneity, use of surrogate outcomes (e.g. biomarkers or response rate), and short follow-up durations.

Of note, the FDA approval of the multi-tumour indication for pembrolizumab was based on combined results from five single-arm studies. It's also worth mentioning that increasing numbers of trials are enrolling patients on the basis of specific biomarkers rather than tumour site, which may provide data regarding consistency of response rates across diverse disease sites. For instance, trials using biomarkers to stratify patients susceptible to response made up 34% of the global oncology trials in 2017. Moreover, real-world evidence (e.g. registry and digital health data) can be useful to inform the natural history of the disease and to inform the effectiveness of the new drug and the comparator (e.g. standard of care).

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?

This may be possible for tumours with the same characteristics and natural history; however, it is important to consider differences in specific mutations among tumours or resistance mechanisms within various cancers, which may preclude the use of this approach.

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?

It's hard to assess the cost effectiveness of PD-1 or PD-L1 checkpoint inhibitors without an economic model. This is because most of the clinical trials include intermediate end points (e.g. PFS or response rate), and often there is no mapping function to link these to more relevant outcomes to decision making (e.g. overall survival).

In terms of modelling, there are two possible approaches:

1. *Standard modelling: Develop a separate model for each cancer type included in the multi-tumour list and perform separate cost-effectiveness analyses to identify the tumour type(s) where the drug is cost-effective. The incremental benefits and costs can be averaged across tumour types based on their relative weights. This approach is time consuming and is not different to the current practice of assessing the cost-effectiveness of drugs by tumour type. Most importantly this approach may not help the PBAC simultaneously capture the aggregate benefits and costs of the multi-tumour drug listings.*
2. *Maximal modelling approach: Develop a model integrating the multiple tumours. This approach uses a single comprehensive model to simultaneously inform cost-effectiveness in multiple cancer types with the possibility of clustering different but related tumours types (e.g. similar natural progression, treatment approach). Furthermore, the model can be structured to allow the estimation of the cost-effectiveness of the individual tumour types. On the grounds of parsimony, simplified sub model(s) using broadly defined health states can be used where appropriate. To better characterise decision uncertainty, this model will be probabilistic (which is expected if we want to extrapolate beyond trial duration). The probabilistic sensitivity analysis can be directly used to efficiently calculate (i.e., in seconds) value of information measures to systematically answer the following questions:*
    1. *Is available evidence sufficient to inform a reimbursement decision?*
    2. *Is collecting additional information is potentially worthwhile?*
    3. *Which information should be collected and for which tumour types?*
    4. *Which risk sharing arrangement(s) should be adopted to strike the balance between early approval and evidentiary requirements (e.g. managed entry program +/- special pricing arrangements +/- rebate).*

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?

The subsidy price can be negotiated based on overall cost-effectiveness (i.e., value for money across types of cancer), decision uncertainty (including value of information) and the proportion of tumour types with modest (and better) benefit. Based on past decisions by the PBAC, we know drugs that extend life are valued more highly than drugs that improve quality of life (e.g. analgesics), and these are valued more highly than drugs which reduce risk of future events (e.g. statins).

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?

This should depend on the safety, effectiveness, cost-effectiveness and decision uncertainty assessments of overall and

individual

Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) are good selection biomarkers.

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.

We agree with this as a general principle for PD-1 and PD-L1 checkpoint inhibitors.

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?

There should be flexibility regarding the evidentiary requirements for rare cancers. A major issue is the difficulty in conducting randomised controlled trials due to ethical considerations and/or recruiting challenges. In this case, fit for purpose evidence should be sought (e.g., rare cancers registry) together with appropriate analytical approaches to reduce bias and clinical opinion to validate results.

One thing to consider is that while each rare tumour that could be treated with PD-1 and PD-L1 checkpoint inhibitors may have a small patient population to merit orphan designation, a drug that can treat multiple types of rare cancers could expand the patient population well beyond the orphan drug population threshold.

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.)

A special meeting may not be required if a general framework/approach to evaluate these agents is developed (e.g., using a "master" economic model as is often used when undertaking post-market reviews of a class of drugs).

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?

The existing framework of Managed Entry Scheme (Managed Access Program) can provide a flexible subsidisation arrangement to reimburse these listings conditional on collecting further evidence. However, the need for feasibility and value of any arrangement should be carefully considered. A number of algorithms have been proposed to guide when a drug should be funded based on collecting further information with or without other risk-sharing agreements. These algorithms are based on Value of Information analysis, which is a systematic and quantitative approach to objectively inform the need for and the value of collecting additional research to reduce decision uncertainty. The approach is now incorporated in the health technology assessment guidelines of certain jurisdictions such as the Canadian Agency for Drugs and Technologies in Health (CADTH) and in the Dutch pharmacoeconomics guidelines.

The conditions governing the implementation of the scheme/program should be clear, transparent and balanced to address the expectations of various stakeholders. Moreover, the potential for delisting a drug if it failed to meet the claimed efficacy or safety should be considered together with clear plans to mitigate the impact of delisting a drug on stakeholders (e.g., managing patients who may be receiving subsidised access and deriving clinical benefit). Withdrawal of conditional funding of a drug when subsequent evidence does not confirm promised benefits may not be well understood or received by the public. In this regard, effective communication with patients and clinicians regarding the conditions and expected outcomes of the scheme is central to its success.

Whether the clinical safety and benefits demonstrated in the evidence collected within a scheme would be maintained over the long term is difficult to anticipate. Even with the successful design and completion of a managed entry program there remains the risk of rewarding the manufacturer for short term benefits which may not persist over the entire treatment duration, especially in treating chronic conditions. One proposed approach to reduce this risk is to ''lease'' the technology for a defined period and to renew the lease as long as the drug is delivering the expected benefit. Such an approach would ensure that the long-term risk is shared between the manufacturer and the PBAC.

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?

NA

Question 14

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

We are not aware of any existing 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?

NA

Question 16

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

We thank PBAC for the opportunity to comment on these matters.