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

Pfizer Australia strongly supports the Federal Government's efforts to proactively review the readiness of Australia's health technology assessment (HTA) system to cope with new, innovative health technologies.

While this particular consultation focuses on PD-1 and PD-L1 checkpoint inhibitor immunotherapies, we cannot ignore the fact that cutting-edge innovation is burgeoning around the world across a number of different therapy areas. This is not the first time, and nor will it be the last time, our HTA system is tested by rapidly evolving science and innovation. It is critical that our HTA system is prepared to support timely and efficient patient access to these new technologies.

This challenge is not unique to HTA – medicine registration processes can be equally impacted by rapidly evolving science. Flexibility in the system is critical. In this context, Pfizer Australia strongly supported the Expert Review of Medicines and Medical Devices Registration and Government's subsequent implementation of the new provisional review pathway.

Accordingly, in addition to PBAC consideration of a pan-tumour approach to PD-1 and PD-L1 checkpoint inhibitor immunotherapies at its special August 2018 meeting, Pfizer Australia strongly recommends that Government consider establishing a more fulsome review of Australia's National Medicines Policy to ensure it remains fit-for-purpose and can keep pace with emerging therapeutic technologies and evolving health delivery systems.

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?

There are a number of potential advantages of the PBAC considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings, including:

- Accelerate patient access to important life changing medications
- Provide clinicians with flexibility in choosing treatment options for patients
- Reduce inequities across tumour types
- Reduce redundancies / inefficiencies created by multiple applications for PBS listing
- Reduce PBAC workload.

It is important to note that any solution for this class of medicine could also potentially apply to other classes of medication/ disease areas.

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?

Pfizer Australia notes two potential disadvantages for the PBAC's consideration:

(i) Complications with regulator

Existing regulatory processes and pathways are not conducive to multi-tumour listings in one registration application. The provisional designation scheme, for example, applies per indication. Therefore, consideration must be given to how changes to HTA processes in this context would intersect with the TGA approval and registration. The PBAC could agree that a certain medicine should be listed on the PBS for multiple cancer types, however, that medicine may have some indications TGA-approved and others not yet approved (or ever approved in the case of rarer indications). This has two important implications:

- Use of a medicine in an indication not listed on the ARTG is categorised as 'off label'. Thus, if the PBAC extrapolated across tumour types without TGA registration, this would impact a sponsor's ability to educate prescribers on the use of the medicine for certain indications, meaning the risk/benefit for certain patients might not be fully understood by prescribers.
- When a medicine is registered for a particular indication, the registration includes the approved dosing and administration. However, these are not always consistent across indications. While not a PD-1/PD-L1 checkpoint inhibitor, Sunitinib, for example, is approved for RCC, GIST and pNET, but pNet has different dosing approved to RCC and GIST. If the PBAC extrapolated across tumour types without TGA registration, how would prescribers know how to use the product without approved dosing and administration instructions for each tumour type?

(ii) Equity

The proposal focuses exclusively on one class of medicine (checkpoint inhibitors) within one therapy area (oncology). There are a number of other therapy areas and classes of medicines that might benefit from a pan-location/multi-indication approach.

Question 3

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

Pfizer Australia seeks clarity on the context of this question. Is Government implying that a pan-tumour/multi-indication approach should only be considered for areas of urgent unmet clinical need?

Pfizer Australia would argue that a definition for 'urgent, unmet clinical need' should be established with input from clinicians and the community, and that the definition might vary between therapy areas. Accordingly, it would be difficult to establish a blanket definition for urgent, unmet clinical need beyond the general terms of a "life threatening or seriously debilitating condition where no other therapies are available or the proposed new therapy represents a major breakthrough". Consideration should also be given to aligning the definition of urgent, unmet clinical need across the TGA and the PBAC.

In the context of oncology, we would consider urgent, unmet clinical need to include (but not be limited to) patient groups with the following broad characteristics:

- Patients who have exhausted standard options inclusive of surgery, chemotherapy and radiation and where there is evidence of efficacy and improved survival with a drug as compared to best supportive care;
- Chemotherapy responses are not durable;
- The disease is expected to progress quickly;
- The patient has been diagnosed with an advanced or metastatic disease; and/or
- Where a durable response is expected with an improved quality of life in comparison with standard of care irrespective of line of therapy.

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?

No comment.

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?

No comment.

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 could be possible for the PBAC to satisfy itself that treatment with a PD-1 or PD-L1 checkpoint inhibitor represents value for money without an economic model that is specific to that kind of cancer, but this would depend on how "effectiveness" is ultimately defined. If, for example, PBAC considers "effectiveness" to include measures beyond cost per QALY (e.g. patient perspective, societal impact, mental health impact of hope, etc.) then it may be feasible to achieve cost-effectiveness standards. Alternatively, consideration could be given to a 'pay for outcomes' approach. This could be particularly relevant to rare cancers where the robustness of the model is challenged by a limited dataset.

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?

No comment.

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?

No comment.

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.

No comment.

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?

It has been widely acknowledged that treatments for rare cancers do not fit comfortably into Australia's traditional HTA framework and this is an issue with which other jurisdictions that implement HTA are struggling. This is largely because robust clinical evidence for rare cancer therapies is extremely difficult to obtain due to:

- Limited number of patients for enrolment in clinical studies (and, in the case of ultra-rare cancers, limited numbers of patients may preclude the conduct of clinical studies altogether, with the evidence base consisting of case reports only);
- A lack of feasibility of performance of randomised controlled clinically studies; and
- Limitations on inclusion of a comparator arm in clinical studies owing to ethical issues.

This means that PBAC submissions for these products are usually unable to meet the rigorous cost-effectiveness criteria of pharmaceuticals to be listed on the PBS, with incremental cost-effectiveness ratios for these products being significantly higher and/or more uncertain than would be acceptable to the PBAC.

A more flexible funding mechanism is, therefore, crucial to ensuring patients suffering from rare cancer receive timely and affordable access to innovative new medicines; patient should not be penalised for the rarity of their condition.

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.)

Pfizer Australia strongly supports the notion of equity as a key tenet of Australia's healthcare system. Accordingly, though we support, in principle, the PBAC's objective of streamlining access to PD-1/PD-L1 inhibitors, we would not support any action to achieve this that would adversely impact access for other medicines. We would, therefore, not support a proposal for the PBAC to set aside one of its limited meetings each year to consider only PD-1 or PD-L1 inhibitors for cancer.

Moreover, considering PD-1 and PD-L1 inhibitors at only one specific meeting each year could adversely impact timely access to these new medicines for patients by unnecessarily delaying submissions – e.g. a sponsor may be ready to submit for a November PBAC meeting, but the allocated PBAC meeting to consider only PD-1 and PD-L1 inhibitors might be scheduled for the following July.

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?**

If limited evidence is available at the time of subsidy, Pfizer Australia notes there may be opportunity to explore the use of mechanisms that already exist within Australia's HTA system to generate the additional data required – e.g. a managed entry scheme or the establishment of registries. In addition, given Australia's small population and limited national digital health infrastructure, consideration should also be given to allow sponsors to submit evidence from overseas real-world registries for this class of medicines.

It is important to acknowledge, however, that for some rarer indications, the collection of gold standard clinical trial data will not be possible (see response to Question 10 above). In this case, the PBAC should consider developing a framework for reviewing real world evidence. In building the evidence base for rare indications, pharmaceutical companies could also consider collecting real world evidence outside of clinical trials, e.g. for compassionate use.

Question 13

(For industry/clinical groups) Clinical study 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?**

A Pfizer–Merck Alliance is in the process of completing clinical trials with PD-1/PD-L1 inhibitor avelumab for a number of indications. A list of these trials is in the table below[1]. We would expect to make an application for subsidy for these indications in parallel with or following listing on the ARTG.

There is currently only one registered indication for avelumab in Australia: metastatic Merkel cell carcinoma

Compound Name	Indication	Phase
Bavencio (avelumab)	2nd Line Non-Small Cell Lung Cancer (Biologic)	Phase 3
Bavencio (avelumab)	1st Line Non-Small Cell Lung Cancer (Biologic)	Phase 3
Bavencio (avelumab)	1st Line Gastric Cancer (Biologic)	Phase 3
Bavencio (avelumab)	Platinum Resistant/Refractory Ovarian Cancer (Biologic)	Phase 3
Bavencio (avelumab)	1st Line Ovarian Cancer (Biologic)	Phase 3
Bavencio (avelumab)	1st Line Merkel Cell Carcinoma (E.U.) (Biologic)	Phase 2
Bavencio (avelumab)	1st Line Urothelial Cancer (Biologic)	Phase 3
Bavencio (avelumab)	Combo w/ PF-04518600 (OX40) for: Squamous Cell Carcinoma of the Head and Neck (Biologic)	Phase 2
Bavencio (avelumab)	1st Line Renal Cell Carcinoma (Biologic) (Combo w/ Inlyta (axitinib)) (BREAKTHROUGH)	Phase 3

[1]Pfizer regularly publishes updates to our oncology pipeline, including a list of current clinical trials. Further details can be found here: https://www.pfizer.com/science/oncology-cancer/pipeline

Compound Name	Indication	Phase
Bavencio (avelumab)	Combo w/ PF-05082566 (4-1BB) for: Melanoma, Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Squamous Cell Carcinoma of the Head and Neck, Triple-Negative Breast Cancer (Biologic)	Phase 2
Bavencio (avelumab)	Locally Advanced Squamous Cell Carcinoma of the Head and Neck (Biologic)	Phase 3
Bavencio (avelumab)	Combo w/ PF-04518600 (OX40) and PF-05082566 (4-1BB) for: Cancer (Biologic)	Phase 1
Bavencio (avelumab)	Combo w/ talazoparib (MDV3800) for: Solid Tumors (Biologic)	Phase 1
Bavencio (avelumab)	Cancer (Biologic)	Phase 1

Question 14

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

No comment.

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?

No comment.

Question 16

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

No comment.