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

Today, technology is bringing patients together across cities, state and countries. There are no secrets and terminology such as off label, repurposed drugs, subsidised medicines, compassionate access is over- ridden by the sharing of information to ensure anyone regardless of where they live can find out which treatment is best for them. Digital platforms of communication are changing outcomes for patients - despair to hope, terminal to survivor. Experiences with side effects are shared and tears fall for strangers when another life is lost.

Immunotherapy has given some patients their lives back and others disappointment when another therapy has failed. In Australia, we have also seen cases of absolute devastation that comes with the knowledge that a treatment could work but getting access is impossible.

However, in the context of this submission it also means that Australian patients are become more aware of medicines and treatments, including immunotherapies, that are working for their cancer type but often with limited or no access in Australia.

As we already know, Australia is not necessarily a place of choice for the establishment of trials and therefore patient access to treatments can be years behind Europe and America. Therefore, PBAC may need to be more open to looking at global evidence to assist with a faster turnaround of decisions and access for Australian patients. It should also be noted that a number of Australian patient groups are members of global networks and we can also provide evidence about patient experiences from our overseas colleagues.

Leading up to the PBS approval of Keytruda for relapsed / refractory Hodgkin Lymphoma access for patients was inequitable and highlighted the need for a fairer process to be established to bring clinical trials and innovative therapies to all patients - not just the lucky ones.

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?

Current advances in research and genomics is giving us information that multi tumour types can benefit from PD1 and PD – LI checkpoint inhibitors. We have entered a new era of how we can determine which cancer will respond to which treatment. PBAC will have the opportunity to make recommendations that are specific to a tumour type rather than a cancer type.

In turn, patients could be spared having treatments that are likely to have no real benefit but because they are approved in Australia this is the only option for them. Potentially more lives will be saved, progression free survival time will be increased, and patients will be living with their cancer rather than dying from it.

By engaging with all key stakeholders PBAC will be able to develop and deliver a system that encompasses some of the unique challenges that we have in Australia in relation to fair and equitable access to medicines.

Via a multi tumour listing approach the Australian health system will be paying for treatments that work giving PBAC the power to give recommendations to ensure the right treatments are given to the right patient at the right time

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?

Whilst there has been research, trials and data showing how immunotherapy can work there is also many questions to be answered, including long term side effects, clinician experience with immunotherapy, patient responses including pseudo progressions and where immune immunotherapy is best placed in the treatment pathway.

Immunotherapy does not work for everyone, but public perception is being buoyed by wonderful responses from some patients across different cancers.

Potentially there are no disadvantages if PBAC considers a multi - tumour listing for the PD-1 and PD-L1 checkpoint inhibitors but how it will be incorporated into our health system in a fair and cost-effective way will be the challenge.

Question 3

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

An urgent unmet need would be when we have the **evidence** that a PD-1/PD L-1 checkpoint inhibitor could work for an Australian patient or subset of patients for a specific cancer/tumour type, but this treatment is not approved in Australia. These patients are missing out on world's best care because they live in Australia.

A second group is where we have **emerging evidence** e.g. phase 2 trials that a PD -1 could work for terminal patients to significantly improve overall survival time. Again, these trials are either not available in Australia or in only 1 or 2 locations.

A third group is where combination therapies with a PD -1 / PD – L1 checkpoint are working but again in Australia patients are missing out because there are no trials here despite the treatments having TGA approval.

A fourth group is where a cancer type/ subtype of a cancer has an identified tumour marker that could benefit from a PD1, but no research has been done for this cancer.

If discussions continue across key stakeholder groups an agreed definition of *unmet need* could be established to identify a priority listing and pathways to access. This could assist with everyone having a clearer understanding of how decisions will be made in the early stages of a pan tumour approach. This will give clarity when communicating within our own groups, the media and the general community.

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?

This is an extremely difficult question because when cancer becomes your reality and you are fighting to survive or you are caring for someone who is not ready to give up – hope is powerful. There are many examples of patients who didn't comply with the statistics and are still alive despite the odds being stacked against them.

A layered approach may give PBAC and key decision makers some real guidance in this area as the budget isn't infinite, but research and trials are giving us evidence where PD 1s are demonstrating efficacy and safety in certain patient population groups.

Denying Australian patients access to a treatment that will work is wrong but giving patients access to a treatment where there is no evidence that it will work also needs to be taken into consideration.

A gap to date has been the capturing of outcomes and adverse events when an Australian patient has access to medicines that are not approved on the PBS for their cancer type.

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?

Provided PBAC is given the correct information about patient selection that has demonstrated evidence and data from clinical trials and patient feedback from Australia or overseas there should be no reason for PBAC to not consider this submission.

Some trials are showing that there are tumour mutations common to different cancers and a PD 1 is working across these cancers.

There are also trials showing that despite the same mutation being on 2 cancers the PD1 is only being effective for one group. This often then leads to further research where an additional treatment is added to make the PD1 more effective.

Therefore, there is an opportunity for PBAC to consider a checkpoint inhibitor across cancer types provided all of the information is made available to them including patient feedback.

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?

Comment only – Research and development costs have been covered for these treatments therefore a lesser price seems reasonable for a pan - tumour approach.

Pay for performance should also be included and tracked.

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?

Out of our scope for 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?

It is our understanding that there is already evidence to show there can be different responses to PD-1 and PD-L1 medicines despite the same biomarker being displayed on different cancers.

However, this doesn't mean this is a reason for exclusion rather a need for evidence for inclusion. Further research is also demonstrating adding a targeted therapy to a PD1 and PD – L1 medicine can improve outcomes for some cancers where there was a limited initial response despite having the same biomarker as a different cancer.

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.

Yes

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?

A pan - tumour approach is not about a specific cancer and no patient group should be advantaged or disadvantaged by this approach. Patient groups may need to be educated about PD1 s and the incorporation of a pan - tumour approval process to ensure their communication to their patient groups is balanced, informed and fair.

Patient groups also need to acknowledge that evidence will be driving change and not emotions as a pan - tumour approach needs to be financially sustainable if we want the most people to benefit in the long term.

Common cancers including lymphoma, bowel and breast also have rare subtypes and therefore we need to ensure that the definition of rare is encompassing common and rare cancers.

There has also been a significant drift away from pharmaceutical companies giving compassionate access to medicines for hard to treat or cancers where there are limited treatments/ clinical trials. Over the last 5- 10 years, the true compassionate access cancers (e.g. rare cancers) are being overlooked due to the access being given to patients that cannot access clinical trials.

The lifesaving drug program in Australia could also be an option for cancer patients where the *right to try* is a focus as opposed to the *right treatment to the right patient at the right time.*

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.)

Due to the significant burden that cancer imposes not just on the health system but also on society it may be more beneficial for PBAC to consider separating cancer from other diseases at PBAC meetings. This is not because cancer is more important than any other illness, but all diseases may ultimately benefit from this approach. This could then

eliminate the need to set aside time for 1 treatment modality for cancer. However ongoing discussions between key stakeholders about PD-1 or PD-L1 inhibitors could identify opportunities and challenges and be scheduled every year to maintain the sharing of information for this treatment.

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?

- Should sponsors be required to collect more evidence?

Yes, if the evidence is available it should automatically be included at the time of the PBAC meeting. If no evidence exists then the treatment does not comply with the current parameters for the approval of medicines.

- What should happen if the new evidence shows the medicine is less effective or has greater safety risks than expected

There are 2 separate questions. If the medicine is less effective, then it shouldn't be subsidised unless there was a subset of patients who are unable to have the standard treatment due to health issues.

Greater safety risks can be influenced by a number of factors. E.g. age of patient, health status, is this a potential cure or to prolong life and patient preference. This was also a huge debate on our closed Facebook page for patients and the discussion ultimately led to this being a choice to be made by the patient in consultation with their doctor.

- 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?

This needs to be part of the initial consultation process before any agreement is reached to ensure there are checkpoints for subsidy, performance and adverse events. Patients should never be disadvantaged if the treatment has been approved and is working for them.

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?

Would be keen to check with our global colleagues and supply this at a later date

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?
Lymphoma Australia appreciates the opportunity to make a submission on behalf of Australian patinets as PD1 and PD – 1 inhibitors will be an ongoing treatment option for lymphoma subtypes.