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

Summary

Lynch Syndrome Australia (LSA) strongly urges PBAC to extend subsidised access to checkpoint inhibitor immunotherapies.

Background

LSA is the only national advocacy group that represents Australians diagnosed with Lynch syndrome and their families. Lynch syndrome (LS) is an inherited gene fault that predisposes the carrier to multiple, primary cancers from a young age. Lynch syndrome is Australia's most prevalent cancer causing gene mutation and it is conservatively estimated by epidemiologists that 1:250 Australians (approx. 100,000 people) have one the identified mutations in a cancer repair gene. It has been estimated that around 4,000 cancers in Australia each year could be Lynch syndrome-associated. Patients with Lynch syndrome have already had experience with a number of immunotherapy PD-1 PD-L1 treatments and treatment combinations.

Immunotherapy and MSI high

Lynch syndrome cancers are always microsatellite unstable (MSI high). Therefore, the population group we advocate on behalf of, has dMMR tumours. In research to-date, some of the most promising responses to both PD1 and PD-L1 checkpoint inhibitor immunotherapies have been people with Lynch syndrome. However:

- Off-trial costs of most immunotherapies approved by the TGA are around $6-$7000 per treatment and recommended dose numbers is generally around 24.
- Indeed, access to clinical trials for people with Lynch syndrome has, to date been severely limited where the average cost (around $6/7000 dollars) per immunotherapy treatment.
    - It is only generally accessible/available to our population group on clinical trial. And, despite the fact that the effectiveness of this treatment is site-agnostic, current trials are mainly restricted to site specific cancers which are rarely the most prevalent sites for LS-associated cancers.
    - Also by the insistence that patience follow 'standard of care' protocol. This means that, in general LS patients must have undergone surgery, radiation and or chemotherapy treatment regimes. These regimes can take a long time and Lynch syndrome tumours are aggressive and generally display rapid carcinogenesis.
    - Anecdotal feedback suggests that off-trial access to immunotherapies is difficult to obtain, even if the patient is prepared to pay.

The combined strictures due to cost and insistence on standard of care protocol for access to clinical trials and the conservatism of treating doctors means that every week, Australians with Lynch syndrome are missing out on treatment which is likely to have good outcomes thanks to their dMMR status.

Multiple cancers, multiple family members

People with Lynch syndrome who develop cancer have on average two primary cancers and can be up to eight in a lifetime It is negligibly under-diagnosed and tens of thousands of Australian families do not know they are at risk. Lynch syndrome cancers are often diagnosed at a young age (under fifty years of age) and it is currently associated with a minimum of 12 tumour types, both rare and common. Since Lynch syndrome is inherited in an autosomal dominance pattern, it is not uncommon for a majority of blood relatives to be lynch-positive.

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?

Lynch syndrome is an inherited gene fault that predisposes the carrier to multiple, primary cancers from a young age.

Lynch syndrome cancers are always microsatellite unstable (MSI high). Therefore, the population group we advocate on behalf of always has dMMR tumours which respond to PD- 1 and PD-L 1 checkpoint inhibitors.

People with Lynch syndrome who develop cancer have on average two primary cancers and can be up to eight in a lifetime. These tumours can be in different sites, it would therefore be prudent to be able to offer effective treatment to these patients regardless of the tumour site.

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?

We do not see any disadvantage to listing PBAC considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings. However, we advocate that these treatments are considered as first line treatments not as second or third line treatments particularly as patients with Lynch syndrome do not necessarily respond well to standard treatment protocols.

Question 3

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

We advocate for all patients with Lynch syndrome tumours in all sites to have access to PD- 1 and PD-L 1 checkpoint inhibitors.

PD- 1 and PD-L 1 checkpoint inhibitors are only generally accessible/available to our population group on clinical trial. And, despite the fact that the effectiveness of this treatment is site-agnostic, current trials are mainly restricted to site specific cancers which are rarely the most prevalent sites for Lynch syndrome-associated cancers.

Off trial costs of most immunotherapies approved by the TGA are around $6-$7000 per treatment and recommended dose numbers is generally around 24.

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?

From our understanding, clinical trials and personal experience indicate the effectiveness of PD- 1 and PD-L 1 checkpoint inhibitors. We appreciate that decisions are required to be based on the evidence but also acknowledge that international regulatory bodies such as the FDA in America have listed PD- 1 and PD-L 1 checkpoint inhibitors for multi tumour use and the PBAC should take this background work into consideration.

It is also important to note that patients when fully explained the risks and benefits of treatment, particularly those with limited long term data should have access to life saving treatment.

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?

Yes. Trials in the USA have demonstrated that immunotherapies are site-agnostic in their efficacy. If the appropriate tumour markers are present, then the efficacy does not appear to depend upon the location or indeed the stage of cancer.

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?

N/A

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?

We disagree with the premise of this question.

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?

Yes, if that biomarker has proven to respond well in previous trials.

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 are not in a position to 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?

Yes, different evidentiary requirements are appropriate for rare cancers. Unfortunately, with rare cancers there is not the population base to undertake large clinical trials.

This is why it is so important to provide access to PD- 1 and PD-L 1 checkpoint inhibitors to all tumour types in which have demonstrated response to this class of drug.

The drug will be cost-effective if the patient has a positive result.

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.)

It is our understanding is that the meeting on the 17th August is a special meeting, therefore this would not be at the expense of other submissions for other medicines.

Moving forward, should the PBAC recommend the current available PD-1 or PD-L1 inhibitors for cancer are listed, all future applications should be considered in the regular meeting agendas.

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?

We are not in a position to comment

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?

N/A

Question 14

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

N/A

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?

N/A

Question 16

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

Please see our comments in the general statement at the start of this response.

We are grateful for the opportunity to make this submission.

LSA would welcome the opportunities to discuss some of these matters in more details with PBAC, in particular given the very short time and limited resources we had to compile a useful response.