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

The development of checkpoint inhibitors has been a major breakthrough for the treatment of cancer. These drugs have had a substantial impact on the survival and quality of life of many individuals with different types of cancer (e.g. melanoma and non-small cell lung cancer).

An approach that simultaneously considers subsidy for multiple cancer types has the potential to result in more rapid and equitable access to checkpoint inhibitors for individuals with cancer, particularly those individuals with rarer cancers. However, this approach may expose some individuals to treatments that are ineffective and potentially harmful if there is a lack of evidence to support their use for certain indications.

The Medical Oncology Group of Australia (MOGA) acknowledges the challenges of an approach that simultaneously considers subsidy for multiple cancer types, particularly when there is not a strong rationale to extrapolate benefits from one cancer type or stage to another, or extrapolate between different checkpoint inhibitors, and when there is no single biomarker to predict benefit that can be used across all cancer types.

Priority should be given to approval of checkpoint inhibitors in rare cancers and in indications where survival outcomes are particularly poor. Such approval should be based on an appropriate level of evidence of benefit.

Please note the responses of MOGA to the questions in this template pertain specifically to the treatment of adult cancers and make no comment on the treatment of childhood cancers.

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 major potential advantages of an approach that simultaneously considers subsidy for multiple cancer types are:

1. More rapid and equitable access to checkpoint inhibitors for individuals with cancer. This will benefit individuals with rarer cancers in particular, where there is an absence, and may always be an absence, of high level evidence for treatment with checkpoint inhibitors.
2. Reduction in the risk of financial toxicity that can result from individuals wishing to access checkpoint inhibitors for indications currently not listed on the PBS (Pharmaceutical Benefits Scheme).
3. The ability to use this approach to build a database of real-world outcomes of individuals treated with checkpoint inhibitors where there is a lack of high level evidence from clinical trials.

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?

The major potential disadvantages of an approach that simultaneously considers subsidy for multiple cancer types are:

1. Some individuals will be exposed to therapies that are not effective and potentially harmful if indications are approved for subsidy when the evidence is very preliminary or absent.
2. Uncertainty about the value for money in certain tumour types and the resultant opportunity cost to the PBS and health system in general.

Question 3

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

There is urgent unmet clinical need in two broad groups of individuals with cancers. These are:

1. Individuals with common cancers with 5-year survival rates less than 20%.
2. Individuals with rare and less common cancers with no or few PBS subsidised treatment options, irrespective of their survival rate. According to Cancer Australia, a rare cancer is defined as a type of cancer that has less than 6 incidences per year per 100,000 population. A less common cancer is defined as one that has between 6 and 12 incidences per year per 100,000 population.[1]

Applications for PBS listing of checkpoint inhibitors with appropriate evidence of clinical benefit in these groups should be prioritised.

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 minimum level of evidence of effectiveness required depends on whether the cancer type is considered common or rare. For common cancers the minimum level of evidence of effectiveness should be a randomised phase III clinical trial. For rarer cancers, or specific subtypes of common cancers, single arm studies may be considered as reasonable as large phase III trials are unlikely to be conducted.

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?

There is not a strong rationale to extrapolate evidence of effectiveness of checkpoint inhibitors from one form of cancer to another. The degree of benefit of checkpoint inhibitors varies vastly between different tumour types. Extrapolation of evidence of effectiveness between late stage or early stage cancers also has little rationale. For example, activity of checkpoint inhibitors in late stage cancers may not equate to an increased chance of cure in early stage cancers.

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?

MOGA acknowledges the difficulties of determining cost-effectiveness without economic modelling for specific indication(s). If the PBAC wished to consider an approach for subsidy of checkpoint inhibitors without economic modelling then established scores of clinical value (e.g. ESMO Magnitude of Clinical Benefit Scale (MCBS), ASCO value framework) could potentially be used for this purpose.[2,3] Price could be linked to scores derived by using one or more of the above scoring systems. For example, if an indication gets an ESMO score of 5 it could qualify for price $X.

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?

MOGA has no comment as to what constitutes a reasonable price for checkpoint inhibitors nor the appropriate threshold of cost-effectiveness. However, MOGA strongly supports a more relaxed threshold for rare tumours where the overall impact on the PBS budget is minimal.

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?

There is no definitive biomarker than can be used to predict benefit from treatment with PD-1 and PD-L1 inhibitors at this stage that is accurate enough across all tumour types. One biomarker with promise is that of tumours with evidence of microsatellite-instability (MSI-high) or mismatch repair deficiency (dMMR), however only the minority of tumours would be determined to be MSI-high or dMMR.[4,5] Evidence of the benefit of pembrolizumab in MSI-high/dMMR tumours irrespective of tumour type has led to FDA approval for this indication. MOGA would support the PBAC considering an application for this indication.

PD-L1 is another biomarker that has been extensively studied. Although it appears that higher levels of PD-L1 expression in some tumour types are associated with higher response rates, tumours that do not express any PD-L1 may still respond to checkpoint inhibition.[6] This and a number of other issues make it currently unsuitable as a predictive biomarker across tumour types.

Other potential predictive biomarkers include but are not limited to: tumours with higher somatic mutation burden, tumour infiltrating lymphocytes, immune gene signatures and microbiome profile.[7] None of these biomarkers are ready for use across all tumour types.

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.

Although some checkpoint inhibitors may be considered interchangeable (e.g. pembrolizumab and nivolumab), at this stage it is probably inappropriate to extrapolate the evidence from one checkpoint inhibitor to another.

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?

MOGA would support the use of lower levels of evidence to support decisions about subsidising drugs with indications in rare cancers. While this may make economic modelling more challenging, their relative clinical value can be ascertained by using ESMO MCBS scores (Version 1.1, Form 3) for rare tumours.[2]

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.)

MOGA does not think a yearly stand-alone meeting is necessary.

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?

MOGA would support collection of more evidence in this situation either in the form of further clinical trials or collection of real-world data (as long as the process of further data collection is not overly burdensome to medical oncologists). If the subsequent collection of evidence is not consistent with the original data used to make a decision about subsidy then it would be reasonable for prices to be re-negotiated.

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?

MOGA is unaware of international models for multi-tumour listing for checkpoint inhibitors although some may well exist. We reiterate that this approach would seem reasonable in individuals with MSI-H/dMMR cancers, based on data available to 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?
N/A
Question 16 Is there anything else you/your organisation would like to add?
MOGA wishes to thank the PBAC for the opportunity to contribute on this matter under consideration. MOGA would be happy to provide further advice to the PBAC if it would be of assistance.

References

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2. Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017
3. Schnipper LE, Davidson NE, Wollins DS, et al: Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received. Journal of Clinical Oncology, 2016
4. Le DT, Durham JN, Smith KN, et al: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357:409-413, 2017
5. Le DT, Uram JN, Wang H, et al: PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. New England Journal of Medicine 372:2509-2520, 2015
6. Gibney GT, Weiner LM, Atkins MB: Predictive biomarkers for checkpoint inhibitor-based immunotherapy. The Lancet Oncology 17:e542-e551, 2016
7. Yarchoan M, Hopkins A, Jaffee EM: Tumor Mutational Burden and Response Rate to PD-1 Inhibition. New England Journal of Medicine 377:2500-2501, 2017