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

MSD is aligned to the two pathways (Recommendation 1: Follow-on pathway & Recommendation 2: Rare cancer pathway) described in the Medicines Australia submission and we have provided further details as to how these might work in practice in Appendix 2.

We note that multiple submissions are being provided to this consultation and wanted to highlight our flexibility with respect to the final approaches to be implemented. Based on our consultation with stakeholders to date, we believe there is enough overlap in interests and ideas to enable a constructive discussion moving forward. Following the PBAC special meeting, we propose that a stakeholder meeting be convened to further work through the options that have been presented to the Committee.

Given the introduction of new expedited assessment pathways implemented by the TGA following the *Medicines and Medical Devices Regulation Review*[1], it seems to be a suitable time to consider new pathways for medicine reimbursement. While the current proposals are specific to PD-1/PD-L1s, these could be considered for other multi-indication therapies in the future if found to be successful. We have described two pathways, both of which are adaptations of existing reimbursement mechanisms, managed entry and pay for performance pricing arrangements. These recommendations can be implemented under the current legislative framework and the PBAC still maintains the right to reject submissions for both streamlined pathways. It should also be noted that the standard PBAC review process will be maintained and can still be used, if desired

Our primary goals are that the following principles can be achieved:

- Timely & equitable access: Resources will be provided upfront to define patient populations, as well as clarify expectations of clinical benefit and cost-effectiveness. As companies will only lodge submissions that meet these criteria, they are more likely to gain initial approval after one PBAC meeting.

  Listing would occur at a pre-agreed anchor price per patient with verification of cost effectiveness to be completed at year 4 (for indications in the 3-year risk sharing deed) to confirm the appropriate subsidy. In the period prior to verification, there will be agreement on a risk sharing arrangement between sponsors and the Commonwealth. The risk sharing mechanism could comprise a genuine risk-sharing arrangement, where the uncertainty is shared equally between Sponsors and the Commonwealth. This could be partly managed by a price volume agreement, whereby rebates are applied according to volume-based tiers. After the verification process, the anchor price is re-adjusted based on the specific efficacy and cost-effectiveness criteria and rebates are paid accordingly.

- PBS Listing is streamlined following a positive PBAC recommendation. Horizon scanning conducted at the start of the agreement would enable a determination of patient numbers and budget caps. A target listing date of 3 to 4 months is proposed from the date of PBAC recommendation for the streamlined pathway.

- Rare Cancer Solution: A rare cancer solution for patients who would not otherwise have access to these therapies using a 'pay for performance' pricing model. Verification of outcomes would be conducted using electronic health data (e.g. the Garvan Genomic Cancer Medicine Program MoST clinical trials, MyHealthRecord)

- Budget certainty: The ability to forecast budget upfront for the PBS listing of immunotherapies leading to greater predictability may be beneficial to the Government. Similar horizon scanning and budget commitment processes have been used overseas (e.g. Italy, UK) and these will be discussed further in Appendix 3.

[1] https://www.tga.gov.au/mmdr

These outcomes would be delivered by an adaptive IO reimbursement process that can be implemented in Australia by considering and adopting the following MSD recommendations:

Recommendation 1: For 'follow-on indications,' which are the subject of RCT-based checkpoint inhibitor development and have demonstrated an initial benefit, the reimbursement process can include early listing at an agreed per patient cost (anchor price) with a post-listing cost effectiveness verification of multiple indications approved over the time period (i.e. up to a 4-year time period). Companies are willing to consider lower entry prices, if subsequently demonstrated value is recognised and reimbursed. Without this, it will be difficult to get support for lower entry prices and earlier access for patients.

Recommendation 2: For rare cancers, which can plausibly be treated with checkpoint inhibitors but have limited data for the purpose of HTA processes, reimbursement should be supported utilising a 'pay for performance' pricing model.

Recommendation 3: A funding framework can be agreed over the next 3 years for immunotherapies to ensure budget certainty and predictability.

Proposed Next Steps

- MSD proposes that a stakeholder meeting be convened to discuss potential options that were raised in the submissions to the Special Meeting.
- A working group to be convened with a broad mix of stakeholders to determine how these proposals can be progressed.
- Pathways to be implemented over a three-year period with verification processes occurring in year 4.
- A pilot process to commence in mid-2019.

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?

MSD agrees with Medicines Australia's response to this question and believes it is possible to achieve the below outcomes while maintaining the principles of the National Medicine's Policy (i.e. equitable and affordable access) and remaining within the current legislative framework of the National Health Act.

The key advantages we see for the proposed pathways are:

- Timely & equitable access
- A rare cancer access pathway
- Budget certainty

How these outcomes can be achieved is described further in Appendix 2, but would entail a streamlined pathway for follow-on indications of common cancers and a pathway for 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?

As noted in the Medicines Australia submission, focussing on special pathways for one class of medicines is a potential concern for stakeholders. MSD recognises that these proposals can be perceived as suggesting one form of disease requires special treatment or access over another. Our submission still fully endorses the HTA and cost-effectiveness principles of the PBS assessment process; however, just as there is a specific program for rare diseases (due to their small populations and life expectancy outcomes), MSD contends that cancer treatment with PD-1s/PD-L1s reflects a similar imperative for expediting treatment access given the lack of alternative treatments and risk of mortality if not treated. Given the volume of submissions that are likely to be lodged for PD-1/PD-L1 therapies in the coming years, developing solutions that can provide access to a range of indications with acknowledgement of the risks associated with early listing could also free resource for other medicines and disease areas.

Notably, the two proposed pathways in this submission are adaptations of existing reimbursement mechanisms, managed entry and pay for performance pricing arrangements. These recommendations can be implemented under the current legislative and regulatory framework and the PBAC still maintains the right to reject submissions for both pathways. It should also be noted that the standard PBAC review process will be maintained and can still be used, if desired.

Question 3

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

MSD is aligned to the proposed definition of unmet clinical need proposed in the Medicines Australia submission, which includes consideration of disease severity, disease prognosis, availability of alternative treatments, and the incremental benefit of the new therapy. The last criteria could be defined using established criteria, such as the ESMO Magnitude of Clinical Benefit Scale (e.g. a score greater than 3 or C).[2]

MSD is also aligned to the patient groups proposed by the Medicines Australia submission, including the following definitions for patients with rare and less common cancer based on RARECARE[3]:

• 'Less common' are defined as those cancers with an incidence of between 6 and 12 (inclusive) per 100,000 Australians per annum;

• 'Rare cancers' are defined as those with an incidence of less than 6 per 100,000 Australians per annum;

• 'Super rare cancers' are defined as those with an incidence of equal to, or less than, 2 per 100,000 Australians per annum, this equates to

[2] http://www.esmo.org/Policy/Magnitude-of-Clinical-Benefit-Scale

[3] Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, et al. Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer. 2011;47:2493–511.

approximately less than 480 Australians per year.

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?

MSD agrees with the proposals provided by Medicines Australia, whereby TGA registration and early randomised clinical trial data would be required to establish effectiveness for Recommendation 1 (Follow-On Indication Pathway).

For Recommendation 2 (Rare Cancer pathway), the evidence and cost-effectiveness requirements would need to be different, given the challenges with conducting clinical trials in rare cancer populations. Indications are expected to be TGA registered; however, it is up to the PBAC and Department of Health to determine whether an unregistered indication could also fit within this pathway – noting the clinical and legal risks of this latter approach. For this pathway, we are proposing a pay-for-performance type model.

Further details of how both of these pathways could operate in practice are described in Appendix 2.

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?

While this proposal is seeking to build on the PBAC's collective knowledge and prior recommendations for the class, it is expected that trial data specific to each indication would still be needed to demonstrate a clinical benefit for the follow-on indication pathway (Recommendation 1). In some instances, there may be evidentiary gaps that are specific to the Australian setting. It would continue to be the PBAC's prerogative to approve reimbursement in a slightly different population based on considerations such as the efficacy of existing and new treatments. However, the post-reimbursement verification process (using further trial data and/or real world evidence) may make decision-making less reliant on the extrapolation of evidence from other indications as compared to the current system.

For the rare cancer pathway (Recommendation 2), a pay-for-performance mechanism has been proposed. While early listing may be based on evidence from other tumour types, the ongoing assessment and reimbursement would be based on direct evidence from the patients receiving treatment.

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?**

MSD thinks it is possible to reach agreement on a risk-sharing mechanism between Sponsors and the Commonwealth that will enable early access across a range of indications while acknowledging the risks associated with early listing (refer to Appendix 2). However, it is likely that this approach will be contingent on both parties tolerating a level of risk that could result in price increases or decreases after verification. Early access at prices that account for uncertainty needs to be met with genuine commitment to pay for demonstrated health outcomes once these are verified.

In Medicines Australia's Recommendation 1 (Follow-on Indication Pathway), only those indications demonstrating an early benefit would be included in the risk sharing arrangement. Cost-effectiveness would then be verified based on longer-term trial data and/or real world evidence and prices would be adjusted accordingly.

In Recommendation 2 (rare cancer pathway), data can be limited and it may not be feasible to construct an economic model meeting the requirements for a PBAC recommendation. Therefore, a pay-for performance approach could be utilised, which would not require an economic model. Notably, this approach has been acceptable in other markets (e.g. Italy).

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?

Recommendation 1: As proposed in Appendix 2 and by MA for follow-on indications, there could be a pre-defined minimum efficacy criteria (e.g. ESMO MCBS score) based on early clinical trial evidence to enter into the streamlined pathway and a 3-year risk sharing deed. This approach would ensure Government pays a clinically justified subsidy price for these indications. Treatments in indications where there was a modest or no additional benefit would be assessed through the standard PBAC review process; thereby providing certainty to Government that they would be paying a clinically justified subsidy price for such use.

Recommendation 2: For Rare cancers, the approach discussed in Appendix 2 (pay for performance type funding with independent assessment of response) would avoid assessments based on limited published evidence and would ensure, as much as possible, that responses to the checkpoint inhibitors are meaningful. Thus, under this approach, the Government would not be required to pay for modest responses to treatment.

Subsidy price prior to verification of outcomes would require a risk-sharing arrangement to be agreed between sponsors and the Commonwealth, where both parties share the initial risk and prices are increased or decreased after verification. Proposed approaches to this are discussed further in Appendix 2.

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?

Where the magnitude of the clinical benefit reaches an agreed standard across cancer types, this could be an appropriate approach. For patients with rare cancers, biomarker-driven approaches may be even more important, as they can allow access to populations for whom there won't be robust clinical trial data. Given that these patients have relatively few other treatment options, there is less harm related to foregone treatment options.

As biomarker-driven trials and indications are becoming more common, further stakeholder consultation of how best to fund these treatments through the existing MSAC and PBAC processes is warranted.

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.

MSD is aligned to the response provided by MA to this question. We would like to highlight the importance of multiple treatment options for patients, allowing for greater individualisation of care. We also feel it is important to maintain value-based assessment, considering some differences have been demonstrated between medicines in the PD-1 and PD-L1 classes.

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?

MSD believes that the existing evidentiary requirements are not always appropriate for rare cancers, where there is often limited clinical trial data.

Recommendation #2 (Rare Cancer pathway) presented here and in the MA submission supports a pay for performance reimbursement model. Registry data to establish efficacy with clear criteria for managed exit. This process is described further in Appendix 2.

We further propose that the RARECARE definition of rare cancer (as proposed in Question 3) be applied to enable a clear understanding of which cancers can enter into the rare cancer pathway.

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.)

MSD agrees with the response provided by MA to support the existing processes for evaluating medicines. We would like to advocate for a process that balances the needs of other diseases and treatments, while providing a more streamlined method of assessment and validation of the data for PD-1/PD-L1s. It is not thought that a separate meeting should be required for these processes

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?**

MSD agrees with the responses provided by MA. We agree that providing more evidence is required when there is an early listing process, as well as for rare cancer access. We further acknowledge that price increases or decreases may be required following verification analyses, and MSD is committed to establishing acceptable managed exit approaches, if these are required.

We have provided further detail of how a post-listing verification process could work for both follow-on indications and rare cancer indications (Appendix 2).

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?**

Please refer to Appendix 1, which includes the template with the requested information. [redacted]

The Keytruda portfolio has evolved as a combination of both MSD internally sponsored trials and externally sponsored collaborative/partnered trials. These trials include both monotherapy and combination trials. Some monotherapy trials may explore more responsive tumours, whereas combination trials often explore less responsive tumours and/or relapsed refractory tumour settings with the intent of increasing sensitivity to PD1 inhibition. At current count, there are 755 clinical trials for Keytruda listed in clinicaltrials.gov (Phases 1 to 4). Some of these trials are funded by MSD, while others are funded by academic and/or industry collaborators (often with additional MSD support).

There are a variety of both high and low prevalence tumour indications, noting that these are generally conducted in conditions where the disease prevalence will allow for eligibility criteria to be met and trial recruitment to occur within a certain timeframe. This means that rare cancers are not usually the subject of randomised control trials or clinical development programs, unless they are included in basket trials.

Question 14

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

Yes. There are aspects of systems in countries, such as Belgium, Denmark, the Netherlands and Italy, which provide useful approaches that could be consistent with the operations of the National Health Act and PBAC processes with some modifications. For further details please refer to Appendix 3 for a detailed summary of international agreements.

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?**
Please refer to Appendix 3 for a detailed summary of international agreements and how could these apply in the Australian context.
Question 16 **Is there anything else you/your organisation would like to add?**
MSD would like to provide a general overview of how we foresee the two proposed pathways functioning and this has been described in Appendix 2.