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 PBAC request for submissions to consider options for PBS subsidy of PD-1/PD-L1 checkpoint inhibitor immunotherapies presents an opportunity, using these medicines as a pilot, to evolve the current system for reviewing the reimbursement of immunotherapies. There may also be learnings from these approaches that can be applied to other innovative medicines which target a particular mechanism and are used to treat multiple or rare cancers. Thus, the proposals for reimbursement of PD-1/PD-L1 therapies may be applicable to other treatments in the future. Given the introduction of new expedited review pathways implemented by the TGA following the Medicines and Medical Devices Regulation Review[1], it seems to be a suitable time to re-consider pathways for medicine reimbursement. We note that this has already commenced within the AMWG Streamlined Pathways project.

Background

Despite having a relatively high incidence of cancer, Australia's cancer survival outcomes have been shown to be among the best in the world.[2] In 2016, Australia's cancer healthcare access and quality scores were ranked 100 (based on a range from 1 to 100) across various cancer types, including non-melanoma skin cancer, colon cancer, testicular cancer and Hodgkin's lymphoma, representing a substantial improvement over the last two decades. This progress is likely due to the health system working effectively across the full spectrum of cancer care – from screening programs through to appropriate end of life care. The use of systemic anti-cancer medicines is a major component of the cancer care continuum and comprises one of the National Cancer Control Indicators.[3]

PD1/PD-L1 checkpoint inhibitors are among one of the most rapidly developing classes of oncology medicine, however they are likely to be followed by other classes of immunotherapies in the near-term future. Based on a review of clinicaltrials.gov (see **Appendix 1**), there are over 900 ongoing Phase 2 & 3 industry-sponsored clinical trials of PD-1 and PD-L1 inhibitors across more than 20 tumour types.[4] Of these, over 600 are due to complete in the next 4 years (2018-2021). The unique nature of the mechanism of action of immuno-oncology treatments, which work on the body's immune system rather than specifically on the tumour, means that the safety profile is broadly similar across the indications explored. The profile of responses has also been shown to translate to durable benefit and OS improvement across tumour types. This leads to a certain "familiarity" with the class by the PBAC and the evaluation teams. To date, the PBAC has reviewed 26 submissions (across 7 indications) for the PD-1/PD-L1 class, enabling an opportunity to use existing experience as the basis for a more efficient way of reimbursing these medicines. This creates an opportunity to further enhance cancer patients' outcomes by allowing for an adaptive system that can meet these growing demands.

In health care systems with formal health technology assessment processes, such as the PBAC process, new cancer medicines must be assessed and approved on an individual indication basis before being reimbursed. This holds even when a medicine has received prior reimbursement for other indications. This repeated assessment of a medicine has not been of concern to date. For example, bDMARDs are broad-acting treatments with multiple PBS-listed indications (i.e. up to 8 indications per medicine). However, these indications expanded over a period of 12 to 15 years. The PD-1/PD-L1 medicines have shown activity across a much broader range of indications, including 7 indications considered for reimbursement in the last three years alone (see **Appendix 2**). Thus, the potential volume of follow-on indications for innovative oncology medicines (especially, but not limited to, checkpoint inhibitor immunotherapy medicines) will lead to a significant workload for both agencies and companies. This may result in significant delays in the approval of treatments and subsequent inequities in access for patients with different tumour types. Furthermore, for patients with rare cancers, the current models for drug discovery, development and reimbursement are not designed in a way that delivers equity of access and improved health outcomes for these patients.[5]

There are two questions to be considered in approaching streamlined and accelerated access to checkpoint inhibitors for people with appropriate cancers.
- Firstly, how can the multiple indications which are being studied in clinical trials be most efficiently assessed to allow

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

[2] GBD 2015 Healthcare Access and Quality Collaborators. Healthcare Access and Quality Index based on mortality from causes amenable to personal health care in 195 countries and territories, 1990-2015: a novel analysis from the Global Burden of Disease Study 2015. Lancet. 2017 Jul 15;390(10091):231-266.

[3] Australian Government. National Cancer Control Indicators. Available at: https://canceraustralia.gov.au/research-data/data/national-cancer-data-strategy

[4] https://endpts.com/an-explosion-of-pd-1l1-checkpoint-studies-is-crowding-the-industry-pipeline-and-thats-a-problem/

[5] Rare Cancers Australia. Rare Solutions: A Time to Act. Retrieved from https://bit.ly/2uBrXq4

> reimbursed access following regulatory approval?
> - Secondly, how can people with rare cancers (which can plausibly be treated with checkpoint inhibitors) that are supported by limited clinical evidence, access reimbursed medicines in a way that is consistent with the National Medicines Policy?[6]

While PBAC processes have been evolving over the years to include changes such as the Managed Access Programs and "pay for performance" pricing arrangements, some of these mechanisms could be further refined to assist with the potential volume of multiple indications for the immunotherapy indications, as well as address the inequity of access for rare cancer patients.

Medicines Australia's contribution to this debate, and answers provided below, will address both of these questions. It is important to note that these two issues are complementary, and different evidentiary requirements and processes are recommended for the two distinct populations (**refer to Figure 1, Question 16**). Given both options are adaptations of existing reimbursement mechanisms, managed entry and pay for performance pricing arrangements, these recommendations can be implemented under the current legislative framework. It should also be noted that the current PBAC process will be maintained and the standard pathway can still be used.

Recommendation 1 (Follow-on Indication Pathway): Follow-on indications which are the subject of RCT-based checkpoint inhibitor development

Due to the broad range of tumour activity, there are extensive clinical development programs relating to PD-1/PD-L1 currently showing activity in more than 30 indications with numerous still under research.[7] 'Follow-on' indications are indications which succeed the lead indications. After the initial approval of a molecule's lead indications, there is a tension created between patients' expectations of faster access, TGA streamlined pathways and the existing reimbursement pathways that require long-term follow-up in order to reduce uncertainty and enable sustainable funding. This paper proposes a process that leverages the Committee's/DoH familiarity with the molecule to achieve a streamlined and accelerated assessment process with cost effectiveness verification done after a pre-specified time period to account for residual uncertainties. Under recommendation 1, it is expected that the level of evidence for follow-on indications is sufficient for PBAC review of efficacy and safety, i.e., an RCT. Resources will be provided upfront to define the populations, as well as clarify expectations of clinical benefit and cost-effectiveness. Therefore, companies are unlikely to lodge submissions for the streamlined pathway that don't meet these minimum requirements and initial approval is more likely upon first consideration.

Some initial thinking on a potential process for reviewing these subsequent indications could be considered with the following:
a) Horizon scanning of all new indications for sponsors of PD-1/PD-L1 medicines to be submitted over a 3-year period with pre-agreement on treated patient numbers to be achieved between stakeholders (i.e. DoH, sponsors, DUSC) for those indications. Three-year horizon scanning periods have been used in overseas agreements (refer to **Question 15**). Identifying indications for which reimbursement will be sought over longer horizon scanning periods is thought to be too unreliable.
b) A stakeholder working group (e.g., Government, sponsors, clinicians, technical experts, patients, evaluation groups) meeting to be held to develop the principles for an Immuno-oncology (IO) cost-effectiveness model at the start of the agreement period.
c) After each PD-1/PD-L1 medicine has had an initial full health technology assessment (HTA) review and positive recommendation of its lead indication, there is an alternative, subsequent HTA pathway that facilitates accelerated reimbursement of follow-on indications where there is a demonstrated clinical benefit (see question 4). Notably, this process has been derived from precedence in other jurisdictions.
d) Agreement on a risk sharing arrangement between sponsor(s) and the DoH in the period prior to verification is captured in a deed of agreement. This can be informed by existing indications for that therapy.
e) Agreement in a deed specifying the requirements for the cost-effectiveness of the new indication and any impacts on pricing of the medicine via the verification process.
f) For each sponsor, post-listing cost-effectiveness verification to occur across multiple indications at the end of the agreement period (i.e. Year 4) using a multi-indication cost effectiveness model based on longer-term trial data and RWE (where there are gaps in RCT evidence). The price will then be re-assessed to reflect the deed of agreement (i.e. increased or decreased) according to the longer-term evidence. Real world data collection should also be conducted in a way that ensures there isn't repetition in the collection of evidence – for example, through a comprehensive registry.

This approach is similar to the current process for Managed Access Programs with some modifications that take advantage of the existing experience with the lead indications as a precursor to decision-making for the follow-on indications. The existing

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[6] "Partners in collaborative agreements to address specific barriers to access for identified groups, including Aboriginal and Torres Strait Islander peoples." (National Medicines Policy, page 4)

[7] https://www.phrma.org/medicines-in-development-immuno-oncology

Managed Access Program approach requires a review and streamlining, potentially under the Streamlined Pathways framework.

Recommendation 2 (Rare Cancer pathway): Rare cancers which can plausibly be treated with checkpoint inhibitors, but have limited data to facilitate robust cost-effectiveness assessment
The 2017 Select Senate Committee inquiry in to R&D funding into low survival cancers attracted an unprecedented number of submissions from patients and patient organisations. One theme[8] which emerged was the request for access to therapeutic options and funding (including both research and long-term sustainable PBS funding) to the same level as the more common cancers. Medicines Australia's submission[9] to the inquiry made a number of recommendations, one of which is particularly relevant for the current consideration: "*develop additional access models for medicines for rare or low survival conditions like … brain cancer*". This recommendation deserves further attention and action because it has the potential to create a system in which people with a rare cancer can access PBS-listed medicines in a PBS-like environment (i.e. national, equitable access; rather than the current situation where access is limited to those who have a well-informed physician close to a clinical trial centre, or to those who are in a financial position to pay privately for access to the non-PBS-listed drug).

Broadly speaking, such an access model for current and future PBS listed medicines, such as checkpoint inhibitors, for patients with rare cancers could comprise:
a) PBAC referral of a medicine to the program, which is based on a definition of what constitutes a rare cancer (e.g. for medicines which are currently PBS listed, where data aren't sufficient to support S85/100 PBS listing for a pan-tumour indication, but where some biological plausibility of activity exists),
b) Agreement between stakeholders on initial treatment and continuing treatment criteria,
c) Agreement on clinical outcome and minimally important improvement to be monitored and assessed. Agreement on a risk sharing arrangement between stakeholders in the period prior to, and then following, agreed clinical outcome assessment which is captured in a legally binding deed of agreement,
d) Establishment of a formalised evidence generation and monitoring infrastructure – ideally one which exists currently,
e) Assessment of agreed clinical outcome by an independent process, probably associated with the monitoring infrastructure,
f) Transparency of the access criteria and reimbursement conditions to patients, families and physicians – specifically, that continued reimbursed access is dependent on achieving the agreed clinical outcome. Medicines Australia seeks input from the PBAC and Department on whether such an approach may be taken on an individual patient use basis as currently exists via the Department of Veterans Affairs and the National Blood Authority.

This approach, which could be similar to a modified pay-for-performance type structure, can be the single most important approach to provide rapid access to checkpoint inhibitors by patients who need them, in a way that is acceptable to Government and the pharmaceutical industry, and transparent to patients and physicians.

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[8] Submission 7, 8, 18, 20, 31, 33, 42, 46, 50, 57, 62, 72, 75, 76, 80, 92, 103, 120, 127, 159, 187, 213, 218, 217, 227
[9] Submission 141

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?

Immunotherapies are a revolutionary development in the oncology treatment landscape and currently include checkpoint inhibitors, immune targets, cancer vaccines, adaptive T cell transfer agents, oncolytic virus immunotherapy and cytokines. Over the next 5 years, anti-PD-1 and anti-PD-L1 agents are predicted to have the greatest impact on cancer therapy across the largest number of malignancies. There is an ability to leverage the uniqueness of the PD-1/PD-L1 checkpoint inhibitors' mechanism of action, which already have demonstrated safety and efficacy profiles across a number of tumour types, to develop a more efficient means of assessing cost effectiveness in follow-on indications and enable access for rare cancer patients. Medicines Australia believes this is possible while still 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.

Undertaking evaluation using the proposed approaches above will enable the following to be achieved:

Equity of timely access for patients:

Cancer remains a national health priority for Australia with the Strategic Cancer Plan for 2014-2019 recommending that all Australians receive appropriate treatment and care, and unwarranted variations in cancer outcomes are reduced.[10] As noted above, the expanding number of immunotherapies and indications may create challenges for Sponsors, the Department of Health and the PBAC in regard to the number of submissions and evaluations. This could lead to inequities in timely access for patients whose tumours are included in smaller, follow-on indications, despite there being evidence of an effective treatment option that works across a patient's entire immune system. The proposed approach allows for timely access while reducing the overall number of submissions. For patients with rare cancers, there is no prospect of accessing new medicines, such as checkpoint inhibitors, unless they are accessed as private prescriptions, or via clinical trials such as the Garvan Genomic Cancer Medicine Program MoST clinical trials.[11] Unless a person can access significant funds, it is very difficult for most people to self-fund newer treatments. Additionally, unless a person has a well-informed physician, resides close to a participating trial centre, and a clinical trial exists, (which is very unusual for rare and less common cancers or RLCC) the prospects of accessing a new medicine via a clinical trial is low. This is unfortunate since, for many of these patients, it is highly biologically plausible that they will experience a response to checkpoint inhibitors. PBAC consideration of the proposed access model is a first step to providing this access in an equitable way. Notably, a key recommendation from the Rare Solutions Report was that stakeholders should: "*Use flexible approaches within existing frameworks (e.g. managed access or risk sharing) to gain access to subsidised medications for super rare cancers in particular.*"[12]

Value based assessment using more comprehensive outcomes data:

One of the main difficulties in assessing cancer medicines is that survival improvements can be challenging to determine, as they may not be the main outcome measured in cancer trials, may be confounded by use of subsequent lines of therapy, or may take a long time to demonstrate. For follow-on indications, the proposed approach allows for verification of outcomes after longer durations of follow-up, which may provide better insights into the long-term benefits of treatment and enhance value-based assessment. This can provide the PBAC more certainty, as it reduces the need to rely on extrapolated outcomes.

For rare cancers, an important advantage of PBAC's consideration of the proposals for access to checkpoint inhibitors for people for rare cancers is to ensure that public funds are used appropriately. Definitions of response criteria require PBAC consideration in conjunction with clinical experts, patients and manufacturers. The increasing use of e-health records in Australia (e.g. MyHealthRecord) may further assist in evidence generation with both of the recommended approaches. Ultimately, the collection of evidence from real world use of the treatment in a rare cancer will allow for a more robust assessment of the medicines value.

Maintain reputation as world leader in HTA and delivery of innovative medicines to Australian patients:

Australia has a long history in using health technology assessment (HTA) to facilitate decisions on the funding of medicines, dating back to 1993. Over the last 25 years, the HTA methodologies used by the PBAC have evolved and will need to

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[10] Cancer Australia. Strategic Plan 2014-2019. Retrieved from: https://bit.ly/2H90ttc
[11] https://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/clinical-genomics/sydney-genomics-collaborative/gcmp
[12] Rare Cancers Australia. Rare Solutions: A Time to Act. Retrieved from https://bit.ly/2uBrXq4

continue to evolve to meet the increasingly complex and dynamic demands of the system. The assessment pathways proposed here can aid in this adaptation, while still maintaining the overarching principles of the PBAC's mandate.

Ability to allocate budget upfront leading to greater predictability:

The current system of assessment by individual tumour type can lead to incrementalism in budget planning. Given the dynamic nature of immunotherapy clinical development programs, conducting horizon scanning and planning upfront can allow for more holistic budget allocation with greater predictability.

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?

Investing in one class of medicines:

The opportunity cost of focussing on one class of treatments that are specific to treating cancers is a potential concern that has been raised elsewhere.[13] If the initial listings for both follow-on indications and rare cancers occur with appropriate risk sharing in place, the system can function appropriately for other medicines and diseases. Furthermore, the approaches described here need not be exclusively applied to the PD-1/PD-L1 class. Given the range of immunotherapies and targeted therapies that are currently being researched and developed, it is likely that treatments with efficacy across a range of tumour locations will be more commonplace in the future. Hence, we foresee the current proposal as an opportunity to pilot and learn from potential solutions for managing future multi-indication treatments of different classes. For patients with rare cancers, there is a broader issue of access that needs full consideration across various therapies in future.

Legislative framework:

It is not clear if the function of the PBAC, as described in the two approaches above, is consistent with the current legislation, or if legislative change will be necessary. However, given that managed access and pay for performance pricing arrangements have been utilised by the PBAC in the past, it is plausible that these approaches are acceptable under the current legislative framework as an HTA review remains an important step of the reimbursement process.

Regulatory approvals for rare cancers:

Current regulatory mechanisms, such as the Special Access Scheme, enable physicians to access medicines for indications not approved or registered by the Therapeutic Goods Administration (TGA). Unfortunately for most patients, cost of therapy remains a barrier to treatment. The recommendations outlined in this submission remove the barrier of funding from accessing medicines not approved/registered by the TGA when the correct regulatory processes, under this circumstance, have been followed. Furthermore, all molecules are assumed to have TGA approval for at least one indication.

While the recent TGA reforms have introduced expedited approval pathways, this does not include a solution for rare diseases. A fit for purpose regulatory pathway for rare diseases still needs to be established. This may be considered within the provisional pathway, with future evidence to be generated in the form of a rare diseases registry'.

Question 3

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

What is urgent unmet clinical need? How should it be established?

The views of patients and physicians are clearly needed to appropriately address these questions. Medicines Australia is encouraged that this consultation has involved multiple stakeholders, including patients and patient groups to ensure their views are represented.

However, the consideration of clinical need should involve an assessment of the 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).[14] Given the TGA's recent development of expedited pathways, it would seem appropriate to align with the definitions applied for the

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[13] Australian Government Department of Health. Submission to the Senate Inquiry into the Availability of New, Innovative and Specialist Cancer Drugs in Australia. March 2015. Retrieved from: http://www.health.gov.au/internet/main/publishing.nsf/Content/govt-response-cancer-drugs

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

provisional and priority review pathways, as well as the recommendations being developed by the Access to Medicines Working Group on Streamlined Pathways.[15]

For which patient groups?

Any patient or patient group can have an urgent and unmet clinical need when the above are assessed. For people with a rare cancer, consideration of the above factors will almost always lead to this conclusion. The definition of what is a rare and less common cancer is therefore a relevant aspect when identifying relevant patient groups. RARECARE[16] defines rare, less common, and super rare cancers as follows:

• '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 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?

Recommendation 1 (Follow-on Indication pathway): For the lead indication, the usual PBAC process would be followed to assess comparative efficacy, safety and cost-effectiveness. For follow-on indications, TGA registration would still be a requirement for each indication as well as early randomised trial data to establish effectiveness. There are various accepted criteria for establishing a minimum clinical benefit (e.g. ESMO MCBS scale), which could be applied before follow-on indications are considered for the streamlined pathway. Clinical groups, such as MOGA, could also have a role in informing this decision. Stakeholder discussions could be held at the start of the agreement to define criteria for establishing clinical benefit and standardised criteria for assessing cost-effectiveness (e.g. as per the diabetes core model). If a treatment does not meet the criteria, sponsors would not pursue the streamlined pathway.

Recommendation 2 (Rare Cancer pathway): This will be a critical question as this pathway is for medicines used to treat rare cancers where the level of evidence available is limited for robust assessment by the PBAC – but in a pay for performance type system, effectiveness is established at the level of the individual. Assessment would be against pre-defined criteria which, ideally, are reviewed by PBAC, and potentially consistent with criteria that apply to the existing PBS indications. As discussed previously, this assessment could be made by an independent third party (e.g. trial clinicians associated with the Garvan Genomic Cancer Medicine Program MoST clinical trials).

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?

Recommendation 1 (Follow-on Indication Pathway): This proposal is seeking to build on the PBAC's knowledge, understanding and prior recommendations for the class to facilitate a streamlined assessment process. Clinical data would be needed to demonstrate a clinical benefit in the setting in which the Sponsor seeks reimbursement, and would also include a rating (e.g. ESMO MCBS scale) that demonstrates clinical benefit. 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. Examples of this sort of decision-making have been seen in previous PSDs.[17] However, the post-reimbursement assessment process (using further trial data and/or real world evidence (RWE)) may make decision-making less reliant on the extrapolation of evidence from other indications as compared to the current system.

Recommendation 2 (Rare Cancer Pathway): This question is less relevant for the proposal for RLCC because of the pay-for-performance type arrangement. Thus, no extrapolations are made beyond determination of response criteria (e.g. cancer free survival at 6 months). Such criteria would be based on clinical, patient level responses and so can be reasonably

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[15] https://www.tga.gov.au/sites/default/files/consultation-expedited-pathways-prescription-medicines.pdf

[16] 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.

[17] Ipilimumab, November 2012 – enabled listing in the treatment naïve setting

consistent between cancer types, or stages of cancer. The indication could revert to standard PBS arrangement once enough data has been collected.

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?**

The approaches described above propose a high-level concept of how reimbursement pathways for indications that meet pre-specified criteria could work. Medicines Australia are willing to work with the Department to refine the details of the proposals.

Resources are devoted at the start of the agreement to define the populations and clarify expectations of the evidence and cost-effectiveness. For follow-on/subsequent indications in the 3-year risk-sharing deeds (Recommendation 1), cost-effectiveness is verified at the end of the agreement period and this could be accomplished using a multi-indication model using pre-agreed principles. Given that cost-effectiveness analysis is typically assessed as the average incremental benefit and cost across a cohort within a tumour type (which may be heterogeneous), it seems reasonable and practical that cost-effectiveness could also be established via a weighted average of incremental benefit and cost across tumour types.

In the case of rare cancers (Recommendation 2), a pay-for performance type approach to medicines access should ideally not require the construction of, or evaluation of, a traditional PBAC-level economic model. This approach, in this population, controls expenditure and maximises value for public money by ensuring funds are spent when response (as a measure of effectiveness) is confirmed. Further, in the population of patients with rare cancers, it is not feasible that an economic model be constructed with the magnitude of data and certainty that traditionally leads to a PBAC recommendation. 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 (Follow-on Indication Pathway): As proposed above 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. Such a conservative approach would ensure Government pays a reasonable subsidy price for these indications. Treatments in indications where there was less benefit would be assessed through the standard PBAC review process; thereby providing certainty to Government that they would be paying a reasonable subsidy price for such use.

Recommendation 2 (Rare Cancer Pathway): For Rare cancers, the approach discussed above (pay for performance type funding plus 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 pay for modest responses to treatment.

In regard to subsidy price, prices for outcomes defined relative to existing subsidised indications are a sensible and equitable starting point for discussions.

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?

Recommendation 1 (Follow-on Indication Pathway): Where there is a proven biomarker for an indication, this could be the appropriate approach. However, this should be guided by the clinical evidence. Given that there is likely to be growth in personalised medicine and tumour agnostic study designs, the framework should allow for biomarker-driven indications to be accommodated in the future. The role and types of biomarkers to identify patients most likely to benefit from immunotherapy is evolving as further evidence is generated, and it will be important to capture this evidence as part of an MES-type arrangement.

Recommendation 2 (Rare Cancer Pathway): This recommendation focusses on securing access to PBS listed medicines, such as the checkpoint inhibitors, for people with RLCC. It is likely that defining the patient genotype or phenotype will provide a sufficient level of biological plausibility such that the use of the checkpoint inhibitor is a reasonable clinical decision. This is particularly relevant for rare cancers when the evidence generated may be in the form of a biomarker-driven, tumour-agnostic basket trial. This should be determined for the medicine, in conjunction with the PBAC, clinicians, patients and the sponsor. Consequently, checkpoint inhibitors should be made available to all patients with RLCC for whom a checkpoint inhibitor has plausible likelihood of effectiveness (as per the answer to question 3). These patients also have relatively few other treatment options, so there is less chance of harm related to foregone treatment options.

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.

Medicines Australia considers that the availability of multiple treatment options in the same class provides a clear benefit for patients, who may respond to, or tolerate better, one medicine over another in the same class. However, it is important that the prices for these medicines be linked to the cost-effectiveness assessments that are proposed as part of recommendation 1, (i.e. at the point of initial assessment and then at the time of validation of cost-effectiveness at the end of the agreed period). The PBAC routinely makes recommendations to the Minister in regard to whether a particular medicine is interchangeable at the patient level.

Medicines Australia's view is that this topic of checkpoint inhibitors for multi tumour usage is neither a stimulus for, nor the correct forum, in which to debate policy on pricing or extrapolation of one checkpoint inhibitor for 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?

The existing evidentiary requirements are not always appropriate for rare cancers, which is why Recommendation 2 supports a pay for performance reimbursement model. Registry data to establish efficacy with clear criteria for managed exit will be applied here.

The PBAC generally takes a traditional approach to the assessment of the value of medicines, focussing on incremental cost-effectiveness ratios (ICERs), which consider only some aspects of 'value' such as survival and quality of life, and budget impact. The PBAC's focus does not include other important 'value' elements of medicines, including productivity gains, reduction in need for welfare payments (such as pensions), benefits for carers and the community, improvements in patient compliance and the importance of progress in disease management. In addition, the current system has difficulty providing access to new medicines for patients with rare cancers where clinical trials are challenging to conduct. This presents equity of access issues for those patients who are diagnosed with a rare cancer compared to a patient who is diagnosed with a more common cancer. Costs and effectiveness, including the wider societal impact (to carers, etc), could be considered outside of a traditional cost per QALY framework, particularly when budget certainty can be guaranteed.

It will be important to have a clearly understood and uniformly applied definition for rare cancers if a different approach is to be taken for these types of rare diseases, in which diseases ICERs are difficult, or may even be impossible, to measure with the rigour required by the PBAC.

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.)

Medicines Australia supports the existing processes for evaluating medicines and believes it is important to balance the needs of other disease areas. Using one of the current primary PBAC meetings (i.e. the March, July, November meetings) to consider only PD-1 or PD-L1 inhibitors for cancer is likely to introduce inequity for other treatments in both the oncology and non-oncology therapeutic areas and potentially have a negative impact on timeliness for access to those treatments. It may also slow down the access to PD-1 and PD-L1 inhibitors if they are only able to be reviewed once per year. This is not a preferred situation for any of the myriad stakeholders.

The primary goals of this proposal is to achieve a streamlined process whereby earlier access is facilitated for follow-on indications with demonstrated benefit , and to create a mechanism whereby patients with rare cancers can get subsidised access to medicines via a non-PBS pathway. If the current proposal works well, this could enhance Department of Health and PBAC resources due to fewer resubmissions.

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?**

The concept of providing further evidence to determine the cost-effectiveness of the initially agreed upon subsidy price is a key component for the proposed follow-on indication pathway, which is similar to the current process for managed access (Recommendation 1). The totality of available evidence needs to be considered, and subsequent evidence collection must be fit-for-purpose (i.e. focus on areas of clinical uncertainty). Sponsors and the PBAC should predefine and agree on clinical outcomes to be achieved in real-world practice with broader education of clinicians and patients about the process. If these outcomes (limits) are reached and cost-effectiveness improves or becomes more certain, the process should allow for a subsequent increase in price. Similarly, if the evidence shows the medicine is less effective or has greater safety risks, the sponsor should bear the risk of enabling ongoing subsidised access to patients already on treatment if the clinician deems this to be in the best interests of the patient. These criteria for funding based on different expectations around efficacy as well as the subsequent actions regarding pricing and reimbursement status should be agreed to upfront with sponsors and captured in a deed of agreement.

Similarly, for people with rare cancers (Recommendation 2) the concept of collecting further evidence, and continued funded access being associated with agreed treatment criteria and clinical outcomes is central to the concept. Again, all possible reimbursement outcomes should be captured in a deed of agreement. However it must be acknowledged that the extent of the data able to be generated in RLCC is unlikely to support the rigorous and certain HTA that is applied in the current Australian system.

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?**

This is a question that is best answered from the perspective of the individual manufacturers in their own submissions to the August Special Meeting. However, the search terms "PD-1 OR PD-L1 OR pembrolizumab OR nivolumab OR atezolizumab OR avelumab OR durvalumab" AND Phase 2, 3 trials were used on clinicaltrials.gov (**Appendix 1**). Of trials due to report in 2018 to 2022, there were 621 sponsor-initiated trials identified across 20 tumour types.

Clinical trial programs follow a consistent path of scientific exploration. Basic research scientists continue to investigate the interplay of mechanisms by which PD-1/PD-L1 inhibition leads to anti-tumour effects. An understanding of this biology is foundational to the investigations, and immunotherapy treatments have evolved to 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 and refractory tumour settings with the intent of increasing sensitivity to PD1/PDL1 inhibition.

While there are a variety of both higher and lower prevalence tumour indications included in these programs, clinical trials are conducted in conditions where the prevalence will at least allow for eligibility criteria to be met and trial recruitment to occur within a certain time period. This means that rare and less common cancers are not usually the subject of randomised control

trials or to a clinical development program. Initiatives such as the Triceps program, which proposes the addition of a rare cohort to existing randomised clinical trials, strive to address this trend.

Question 14

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

Please refer to Question 15

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?

Various initiatives are being considered overseas. We have provided a high-level summary of some of these below. While many of these agreements would not fit within the Australian legislative requirements, there are elements (e.g. initial horizon scanning of upcoming indications) that could be quite useful locally.

	Belgium	Denmark	Netherlands	Germany	Italy
New indication delay to Market Access	Up to 30 days	Up to 60 days	Immediate	Immediate	Immediate (if deemed innovative)
Form of value assessment for each new indication at launch	None, available in one month	Mini HTA	Abbreviated HTA	None, available in one month	Risk-sharing, payment by results, Fee for efficacy
Form of agreement	2-tiered volume based discount	PVA	PVA	None	MEA
Duration of agreement	2+1 years	2+1 years	3 years	NA	2 years
Budget allocation	✓ For IO products – €200 M (2018)	No	✓ Product specific	✓ Product specific	€ 1 billion drug fund for innovative therapies
Price	Price based on volume tiers	Price based on volume tiers	Price based on volume tiers	Volume-weighted average price per indication	Net price for each indication with payback depending on performance
Budget cap + payback	✓	No	✓ Product specific	✓ Product specific	✓ Product specific
Any re-assessment of new indication after launch	✓ On-going. CE study required to show impact on all indications	Possible, for any uncertainties in assessment	Possible, for any uncertainties in assessment	✓ Comparator based value assessment within 1 year.	Possible, if MEA is re-negotiated

CE=cost-effective; MEA=managed entry agreement; PVA=price volume agreement

Question 16

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

Figure 1. Proposed Review Pathways for PD-1/PD-L1 therapies
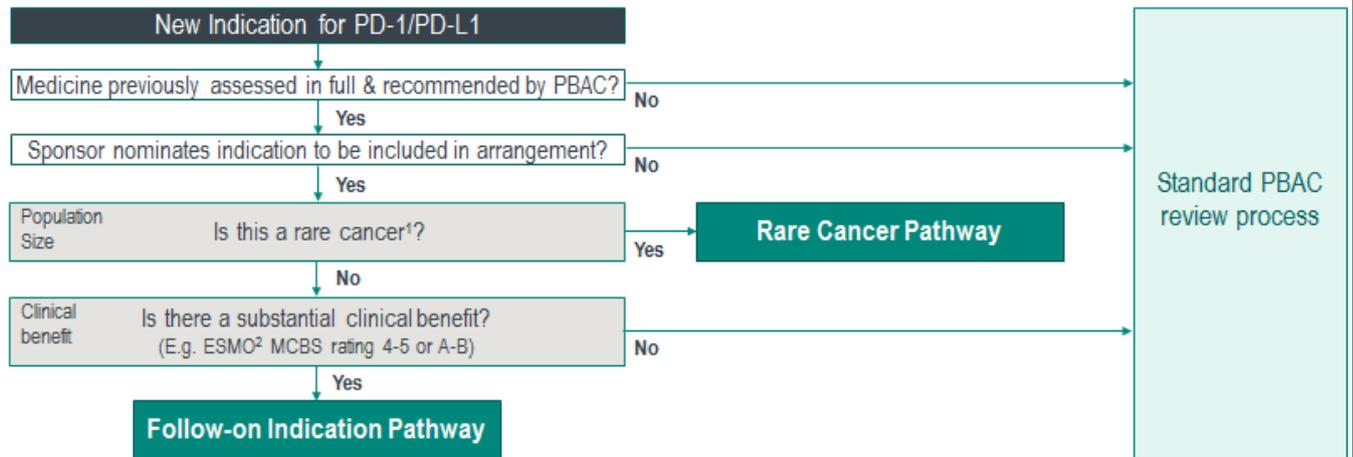
1. Rare cancer definition: less than 6 per 100,000 population
2. Assessment of clinical benefit could be done using ESMO Magnitude of Clinical Benefit Scale (MCBS) or similar, and could involve independent clinical input (e.g. MOGA)