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 South Australian Medicines Evaluation Panel (SAMEP) was established in 2011 as an expert standing committee of the South Australian Medicines Advisory Committee (SAMAC) to ensure that all public hospitals provide a consistent approach to the management of High Cost Medicines. The SAMEP is convened by the Medicines and Technology Programs branch, within the System Performance and Service Delivery division of the Department for Health and Wellbeing. The SAMEP is aware that Drug & Therapeutics Committees (DTCs) are contending with the issue of use of the PD-1 and PD-L1 checkpoint inhibitors as first or later line treatment for tumours including, but not limited to, requests for metastatic colorectal cancer (microsatellite instability high), non-small-lung cancer, metastatic hepatocellular carcinoma, pancreatic cancer, mesothelioma, metastatic pulmonary adenocarcinoma and triple negative metastatic breast cancer. These agents come at a substantial cost to health systems but are often unregistered for the proposed indication and/or are have limited evidence to support them. The argument for availability on an individual patient basis is often compelling; however, consideration of such requests is complicated by the fact that biomarkers that might predict response are not binary and can have a dynamic expression. The relationship between biomarkers and treatment response to PD-1/PD-L1 checkpoint inhibitors is extremely complex and difficult to evaluate at the local level without significant resources. The SAMEP would welcome national evaluation of these complex issues.

In the absence of good quality evidence, and where it has been identified that there is a robust case for accelerated or expedited access in particular populations, it is important to ask what alternative or surrogate evidence could be used to inform a reimbursement decision. It may be possible to use biochemical data in the absence of pharmaceutical data to inform on the relationship of the immunotherapies with the antigen, or of the receptor and ligand on a case-by-case basis, and thereby to extrapolate benefits from one population to another. The SAMEP is of the view that if public subsidy is made on the basis of such a consideration that the validity of the biomarker, and of any extrapolations, are expressly examined. The SAMEP also notes that, whilst technically beyond the remit of the PBAC, it would be relevant to consider how the Australian government might encourage or facilitate the collection of appropriate data to support subsidy considerations.

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 SAMEP view is that PBAC consideration of these issues would have the following advantages:

- The relationship between biomarkers and treatment response to PD-1/PD-L1 checkpoint inhibitors is extremely complex and difficult to evaluate at the local level without significant resources. For selected patients it is clear that these therapies might provide significant benefit. However, the predictive value of PD-L1 may not be the same across different tumours (Carbognin et al., 2015). Additionally, a certain level of PD-1/PD-L1 expression may be more or less relevant depending on the therapeutic agent (e.g. use of companion diagnostic with some agents and not others). State-based decision makers believe that a consistent, robust approach to considering PD-1/PD-L1 checkpoint inhibitors at the national level could be helpful in resolving some uncertainties.
- When considering reimbursement or public funding it is generally accepted that new therapeutic agents that cost more than currently available treatments also need to demonstrate additional benefit, and that the benefit is sufficiently large to justify the additional expenditure. PD-1/PD-L1 checkpoint inhibitors represent a significant, and increasing, source of expenditure at the state level. National level evaluation would facilitate population level analysis of value for money that is beyond the capacity of any State to make.
- Overestimation of clinical benefit (common with immature or low level evidence) can result in patients receiving ineffective or sub-therapeutic products and/or exposing patients to unknown adverse effects of treatment. SAMEP would welcome the PBAC bringing to bear their knowledge and experience with evaluation to this problem with regards to the PD-1/PD-L1 checkpoint inhibitors.
- Within South Australia significant attention is given to ensuring consistency and equity of access to high cost medicines. Due to the complexity of the evidence for PD-1/PD-L1 checkpoint inhibitors and the high cost of agents the SAMEP is acutely aware that patients might face inequitable access to treatment. Research demonstrates that Australian medical oncologists frequently discuss and prescribe drugs that are not publicly subsidised, and that they are concerned about patients experiencing financial hardship and stress (Karikios, Mileshkin, Martin, Ferraro, & Stockler, 2017). In South Australia, we are aware that a number of patients have self-funded their treatment with PD-1 and PD-L1 checkpoint inhibitors whilst in other cases the cost has been borne by the state or shared between patients, hospitals and sponsors. The SAMEP is troubled by this situation and would welcome a consistent national approach to addressing this issue.
- The PBAC could provide a set of standardised targets and thresholds that could be applicable to other drug classes.

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 SAMEP view is that PBAC consideration of these issues *may* have the following disadvantages:

- It is not clear that there is a sufficiently robust understanding of the function of PD-L1 expression as a predictor of response to checkpoint inhibitors; some evidence suggests that up to 15% of PD-L1 negative tumours might exhibit response to checkpoint inhibition (Grigg & Rizvi, 2016; Sunshine & Taube, 2015) whilst recent FDA alerts indicate that in PD-L1–low expressing platinum-eligible urothelial carcinoma monotherapy with PD-L1 checkpoint inhibitors might result in decreased survival relative to standard care.

The SAMEP concern is that broad decisions on the basis of early evidence might either:

- Result in availability of PD-1/PD-L1 checkpoint inhibitors in too broad a patient population, thereby increasing risks of patient exposure to sub therapeutic treatment.
- Result in availability that is too restrictive, thereby possibly excluding patients from effective treatment.

- Although multiple tumour listings for PD-1/PD-L1 checkpoint inhibitors is in some respects a novel idea the SAMEP is uncertain as to why the proposal should not be subject to the same evaluation standards as other medicines considered for public subsidy in Australia.
- The SAMEP is unclear about the implications of giving special consideration to PD-1/PD-L1 checkpoint inhibitors for public subsidy. Any alternative pathway should be structured in such a way that it can inform processes for other drug classes in the future, if and when needed.
- The SAMEP is confident in the ability of the PBAC to contend with these issues.

Question 3

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

The FDA (Food and Drug Administration, 2014) provide the following which could provide a useful framework, where and unmet clinical need is *"a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs).*" For most conditions for which treatment is not curative it is largely accepted that there is an unmet clinical need. The FDA also outline the following situations in which a treatment might serve an unmet clinical need (Food and Drug Administration, 2014):

- If there is no available therapy for a serious condition, there is clearly an unmet medical need.
- Where there is an available treatment the following could be considered to address unmet needs:
  - Treatment which effects on an important outcome of the condition that is not known to be influenced by available therapy
  - Is superior than an available therapy with respect to an important outcome
  - Or is similar to an available treatment with respect to important outcomes whilst avoiding serious toxicity associated with available treatment
  - Has an effect on an important outcome for patients who have failed on or who are contraindicated for available alternatives
  - Provides safety and efficacy comparable to those of available therapy but has a documented benefit, such as improved compliance, that is expected to lead to an improvement in important outcomes

SAMEP makes the following observations:

- Unmet clinical needs are by definition all urgent, they represent opportunities for improved length or quality of life and their relative importance or urgency is a subjective matter.
- Unmet clinical need exists at the patient and population level, it is felt acutely by individuals as well as by decision-makers considering the needs of the populations they serve.
- Unmet clinical need is a broad concept and its impact is a measure of the severity of the medical condition (and therefore the consequences of treatment) as well as the availability of effective treatments. In the context of cancer, particularly in rare cancers and/or metastatic or advanced disease there is an unmet clinical need for treatments which offer durable response or the possibility of cure.
- PD-1/PD-L1 checkpoint inhibitors may offer this for some patients and therefore represent an improvement over currently available therapies; however, the SAMEP view is that there is also an unmet clinical need in terms of the appropriate selection of patients likely to respond to these agents (Grigg & Rizvi, 2016; Sharma, 2016).
- The ability of a treatment to serve an unmet clinical need is dependent on being able to accurately identify

patients who would benefit from treatment. For example, the KEYNOTE-361 and IMVIGOR-130 experience of decreased survival relative to chemotherapy in patients with metastatic urothelial cancer and low PD-L1 status highlights caution and the need for appropriate cut-offs for access to PD-L1 checkpoint inhibitors.

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?

SAMEP wishes to note:

- Appropriate trial design for regulatory approval purposes and for reimbursement purposes differ in important respects. For regulatory approval (a precursor to reimbursement approval) it can be sufficient to demonstrate acceptable safety and to confirm expectations regarding treatment effect i.e. pathological response to treatment. In this context single arm trials in modest patient numbers might be acceptable to regulators.
- When considering reimbursement or public funding it is generally accepted that new therapeutic agents that cost more than currently available treatments also need to demonstrate that they demonstrate an additional benefit, and that the benefit is sufficiently large to justify the additional expenditure. The SAMEP view is that the minimum evidence requirement for public subsidy should involve comparative evidence of robust nature or, involve evidence that is amenable to an analysis in which valid comparisons between novel and standard treatments can be made.
- It is often argued that randomised controlled studies cannot be undertaken due to the inability to enrol sufficient patient numbers, prohibitive costs, or ethical problems with randomisation (presumption of lack of clinical equipoise). However, the SAMEP contends that assurance that a medicine is actually effective is a moral imperative and that promising early results should be the subject of confirmatory subsequent studies.
- Not all novel treatments offer therapeutic advantage and when considering the context of cancer treatment it is crucial that expectations are not unfounded.
- As per the current PBAC guidelines, nonrandomised studies may provide useful information in the following situations:
    - when it is unethical to conduct randomised trials (i.e. when the treatment effect is extraordinarily large in observational studies and so equipoise is not achieved)
    - when randomised trials are not feasible (i.e. when the disease or condition is rare)
    - when rare adverse events cannot be feasibly captured within the duration of a randomised trial (provide nonrandomised study data in addition to randomised trial data)
    - when eligibility criteria for the trial are very restrictive, meaning that the applicability of the treatment effect to the target population is unknown (provide nonrandomised study data in addition to randomised trial data).
- The SAMEP is not aware of any compelling argument as to why the evidence standards to support subsidy of PD-1 and PD-L1 checkpoint inhibitors should be different to those for other rare or serious conditions.
- Drug sponsors stand to gain financially through patient access to medicines, however, if a medicine is made available on the basis of limited evidence the following should be considered:
    - Facilitating early access can disincentivise investment in further research by sponsors; and, means that early adopters bear the burden of financial and health risk associated with the medicine.
    - Patients share the risk, with payers, of unproven medicines. There are public expectations that approved or reimbursed medicines are safe and effective, it is important that if less evidence is required for reimbursement that patients understand the consequent implications for safety and effectiveness of a particular agent.
    - Overestimation of clinical benefit can result in patients receiving ineffective or sub-therapeutic products and/or exposing patients to unknown adverse effects of treatment. If patients receiving access through reimbursement schemes are not enrolled in trials then important information about benefit and risk is not captured.

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?

The SAMEP is of the view that the PBAC and its evaluators are best placed to examine the validity or not of such extrapolations. It is the view of the SAMEP that whether such extrapolations are feasible and valid should be expressly examined by the PBAC.

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 SAMEP is of the view that the PBAC and its evaluators are best placed to consider this issue.

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?

The SAMEP is of the view that the PBAC and its evaluators are best placed to consider this issue. The SAMEP understands that the PBAC is tasked with considering value for money and the SAMEP is not of the view that the consideration for PD-1/PD-L1 checkpoint inhibitors should be treated any differently in terms of value for money than other cancer therapies.

Question 8

Do you/your organisation think PD-1 and PD-L1 medicines should be made available to all patients whose cancers display a particular biomarker? Why? Which biomarker?

It is the view of the SAMEP that whether there is sufficient evidence to make PD-1/PD-L1 checkpoint inhibitors available on the basis of biomarkers should be expressly examined by the PBAC and the MSAC. The SAMEP is of the understanding that since the value of a biomarker is inherently dependent on the sensitivity and specificity of associated tests that such a consideration would in fact be a co-dependent consideration and that the MSAC would likely be involved. The SAMEP view is that the role of biomarkers in patient selection for checkpoint inhibitors is an extremely important question.

The SAMEP notes that:

- With respect to certain PD-1 and PD-L1 checkpoint inhibitors regulatory approval has been linked to the results of validated tests with different tumour proportion score thresholds at different lines of therapy.
- Different checkpoint inhibitors are associated with different diagnostic assays, the interchangeability of assays and checkpoint inhibitors requires evaluation.
- It is not clear that the relationship between PD-L1/PD-1 expression and response can be extrapolated from one PD-1 /PD-L1 checkpoint inhibitor to another.
- For microsatellite instability high (MSI/MSI-H) testing the implications of test result for choice of therapy might be different again and the SAMEP note the Royal College of Pathologists of Australia view that testing might be particularly relevant in colorectal cancer.
- It *might* be that a combination of biomarkers for example PD-L1/PD-1 expression and high tumour mutation burden performs better as a patient selection tool than a single biomarker, whether this holds true across

different types of tumours or different checkpoint inhibitors is uncertain.

- On balance the SAMEP would be cautious regarding suggesting a single biomarker could be used across multiple tumour types, the SAMEP would also be cautious about extrapolation from one checkpoint inhibitor to another.
- A decision as to the usefullness of any particulr biomarker should only be made once that biomaker(s) has been identified, and all basic science and clinical data is available for review.

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.

The SAMEP is of the view that the PBAC and its evaluators are best placed to consider this issue. It is the view of the SAMEP that whether such extrapolations are valid should be expressly examined by the PBAC.

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 SAMEP is of the view that the PBAC and its evaluators are best placed to consider this issue. It is the SAMEP understanding that it is rare that evidence submitted to the PBAC is ideal or can adequately speak to all relevant clinical questions. The SAMEP understands that the PBAC decision making requires judgment, and that the significant experience of the PBAC in dealing with uncertainties will inform any judgement on PD-1/PD-L1 checkpoint inhibitors. The SAMEP is not aware of any compelling argument as to why the evidence standards to support subsidy of PD-1 and PD-L1 checkpoint inhibitors should be different to those for other rare or serious conditions.

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.)

The SAMEP is not aware of any reason why the assessment of PD-1/PD-L1 checkpoint inhibitors should be considered separately to other medicines under evaluation by the PBAC. The SAMEP wishes to note that there are many rare diseases for which novel treatments are becoming available.

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 SAMEP contends that assurance that a medicine is actually effective is a moral imperative and that promising early results should be the subject of confirmatory subsequent studies. The SAMEP view is that this should apply to any listing where subsidy is provided with substantial uncertainty regarding benefits and harms.
- Sponsors stand to gain financially through patient access to medicines, and, if a medicine is made available on the basis of limited evidence the following should be considered:
    - Facilitating early access can disincentive investment in further research by sponsors; and, means that early adopters bear the burden of financial and health risk associated with the medicine. A requirement for evidence collection can help to mitigate this risk; however, the type of evidence to

be collected needs to be considered carefully.

- Patients share the risk, with payers, of unproven medicines. There are public expectations that approved or reimbursed medicines are safe and effective, it is important that if less evidence is required for reimbursement that patients understand the consequent implications for safety and effectiveness of a particular agent. There should be explicit consideration of how consent could be considered might be required.
- Overestimation of clinical benefit can result in patients receiving ineffective or sub-therapeutic products and/or exposing patients to unknown adverse effects of treatment. If patients receiving access through reimbursement schemes are not enrolled in trials then important information about benefit and risk is not captured.
- If a medicine is less effective or has greater risks than anticipated there should be provisions for disinvestment. Further the price negotiated for any medicine should be commensurate with the benefit it provides, if the expectations associated with treatment are not met then it follows that pricing arrangements should change.

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?

Not applicable

Question 14

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

The SAMEP does not have a perspective on this.

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?

Not applicable.

Question 16

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

Monoclonal antibodies against CTLA-4 and PD-1/PD-L1 are increasingly becoming available across a range of indications and have given rise to immune-related adverse events (irAEs) characterised by T-cell response directed at healthy tissue. In South Australia the treatment of immunotherapy induced colitis is of particular concern. Evidence indicates that colitis is both a frequent irAE and a serious, potentially life-threatening consequence. Most cases are treated initially with steroids; however, up to half of all patients might be considered steroid refractory. In South Australia it has been proposed that other expensive biological agents should be used to treat steroid refractory or steroid dependent colitis including infliximab and vedolizumab. Further, sponsors of PD-L1/PD-1 checkpoint inhibitors recommend the use of such biological agents for the treatment of adverse events and patients enrolled in trials generally have access to these medicines with cost born by sponsors. Once such agents are available on the PBS access to biological agents for colitis is determined on the basis of IPUs and the cost is borne by hospitals. The SAMEP is also aware that other, less common but also severe irAEs such as pneumonitis are also being treated with

biological agents. Evidence demonstrates that irAEs are associated with significant costs in the form of: inpatient stays, diagnostic investigations, biological agent costs and specialist opinion costs. Further, that colitis in particular can be associated with long inpatients stays (Yousaf et al., 2015).

It is the view of the SAMEP that any evaluation of PD-L1/PD-1 checkpoint inhibitors takes into account the costs of managing such irAEs.

Citations

Carbognin, L., Pilotto, S., Milella, M., Vaccaro, V., Brunelli, M., Calio, A., . . . Tortora, G. (2015). Differential Activity of Nivolumab, Pembrolizumab and MPDL3280A according to the Tumor Expression of Programmed Death-Ligand-1 (PD-L1): Sensitivity Analysis of Trials in Melanoma, Lung and Genitourinary Cancers. PLoS One, 10(6), e0130142. doi:10.1371/journal.pone.0130142

Food and Drug Administration. (2014, May 2014). Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics Retrieved from https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

Grigg, C., & Rizvi, N. A. (2016). PD-L1 biomarker testing for non-small cell lung cancer: truth or fiction? Journal for ImmunoTherapy of Cancer, 4(1), 48. doi:10.1186/s40425-016-0153-x

Karikios, D. J., Mileshkin, L., Martin, A., Ferraro, D., & Stockler, M. R. (2017). Discussing and prescribing expensive unfunded anticancer drugs in Australia. ESMO Open, 2(2), e000170. doi:10.1136/esmoopen-2017-000170

Sharma, P. (2016). Immune Checkpoint Therapy and the Search for Predictive Biomarkers. Cancer journal (Sudbury, Mass.), 22(2), 68-72. doi:10.1097/PPO.0000000000000185

Sunshine, J., & Taube, J. M. (2015). PD-1/PD-L1 inhibitors. Current opinion in pharmacology, 23, 32-38. doi:10.1016/j.coph.2015.05.011

Yousaf, N., Davidson, M., Goode, E., Thomas, C., Hung, R., Gore, M., & Larkin, J. (2015). The cost of ipilimumab toxicity: a single-centre analysis. Melanoma Res, 25(3), 259-264. doi:10.1097/cmr.0000000000000158