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

We appreciate the opportunity to comment on the significant unmet need to improve survival, especially in cancer types where current approaches have not resulted in durable responses or long-term survival. Addressing the unmet need in multiple cancer types requires development of rational immunotherapy regimens. These regimens may involve the use of one or more immunotherapies in combination initially to achieve objective responses, followed by a defined maintenance period with one of the two immunotherapies to prolong survival.

Proposals to negotiate subsidy prices based on monotherapy uses of PD(L)1s will be inadequate and potentially misleading when these same PD(L)1s are assessed based on their use in multi-drug regimens. PD(L)1s perform differently both as monotherapy and in combination (see responses to Questions 5 and 9). As a result, the value of a PD(L)1 cannot be separated from the multi-drug regimens in which they are expected to be used. To ensure appropriate consideration is given to the effectiveness and cost of health technologies such as PD(L)1s in multiple cancer types, we encourage the PBAC to continue to enable indication-specific value assessments to occur (notwithstanding other questions in this set that relate to extrapolation of evidence, where there may need to be consideration to population need and expected paucity of evidence to determine suitability). There are known modelling issues that may occur with multi-drug combination therapies (depending on the medicines and circumstances of use), and future thought needs to be given to the appropriate valuation of the benefit of these therapies.

Amgen is engaged and committed in identifying approaches that will help HTAs address the complexity of multi-drug regimens, and has experience with these challenges both with our currently marketed therapies as well as our early oncology pipeline. To this end, we have focused our responses in this template on Questions 5, 7, 8, and 9, which elaborate on the limitations of extrapolating evidence of PD(L)1 efficacy, across cancer types, monotherapy and regimen use, and distinct PD(L)1s which may perform differently in the real world.

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?

Not answered.

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?

Please see responses to Questions 5 and 9.

Question 3

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

Not answered.

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?

Please see response to Question 5.

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?

To address unmet needs in multiple cancer types, PD(L)1s are expected to be used in regimens including other immunotherapies, chemotherapies, and/or modalities.

While biological plausibility is an attractive concept, care should be taken with appropriate consideration of extrapolation, especially when applied to value assessment of regimens including a PD(L)1 component in different tumours, lines of treatment, and settings.

We acknowledge the need to ensure evidence generation requirements do not delay listing of treatments that may benefit patients with rare tumours. Rather than extrapolate evidence across tumours, coverage with evidence development and managed entry agreements may provide a more appropriate and value-based approach to extend the benefits of PD(L)1s and PD(L)1-containing regimens to patients with low-prevalence tumours, who may require longer trials to demonstrate potential survival benefits.

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?

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 best approach to ensure patients have access to potentially lifesaving treatments is to assess the value of emerging, novel treatment approaches, which cannot be reduced to the sum of their parts alone. Methods for assessing cost effectiveness should be specific to the unmet need and the strength of clinical evidence demonstrated as a result of the overall treatment approach. In assessment of therapies in combination (for PD(L)1 and other combination therapies, traditional cost-effectiveness analysis may be insufficient to demonstrate societal value, and alternative approaches to valuation may be important to consider.

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?

Multi-drug immunotherapy regimens will play a critical role in addressing the unmet need for durable responses and long-term survival in multiple cancer types. The role of biomarkers in predicting response to PD(L)1-containing regimens is currently under investigation. Tumour-agnostic biomarkers have not been the basis of any accelerated approvals for such regimens to date. However, where evidence is generated to suggest that biomarkers may be a relevant method of assessing benefit, future methods should allow for reimbursement indications to be considered with the evaluation framework.

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.

Extrapolating evidence across PD(L)1s lacks foundation in evidence and may attribute value inappropriately. The question is portraying PD(L)1's conceptually like a generic or biosimilar medicine, which for other F1 medicines would not currently be considered equitable. Important differences may exist between therapies, and scientific method allows for such differences to be potentially portrayed (or not, as the case may be). *Prima facie* evidence for effect should at least be demonstrated. Furthermore, variability in real world use and effectiveness limits the applicability of trial evidence for one PD(L)1 to another, or several PD(L)1s. In particular, trials of PD(L)1s as monotherapy can be subject to differences in the available standard of care for the comparator arm at the time the trial is conducted. These differences may partially explain why some PD(L)1s have not met their primary trial endpoints in patient populations, when other PD(L)1s have demonstrated meaningful benefits in the same indication and biomarker-defined sub-group (for example, based on concordant levels of high PD-L1 expression). For example, the anti-PD-L1 avelumab did not meet its primary endpoint of improving overall survival vs. docetaxel in a trial in patients with non-small cell lung cancer previously treated with chemotherapy, despite the success and U.S. FDA approval of other PD-L1s (atezolizumab) and PD-1s (nivolumab and pembrolizumab) in this indication. Extrapolating evidence of efficacy from other PD-L1 or PD-1 therapies to a treatment like avelumab in this example could create an imbalance between the listing recommendation and the strength of supporting evidence.

Extrapolating evidence across the PD(L)1 class will also create challenges for value assessment of PD(L)1s expected to be used in tailored, rational multi-drug regimens, and will undervalue their potential to deliver appropriate care. The value of PD(L)1 used as part of a multi-drug regimen in one tumour may be different than in another tumour, line of treatment, or setting (adjuvant vs. metastatic). It cannot be assumed that the PD(L)1 component contributed the same efficacy to the regimen across multiple cancer types, treatment lines, or settings.

In addition, prolonging survival with a combination does not necessarily mean continuing treatment with both components of the combination until disease progression. Different combinations will use different doses, treatment durations, etc. specific to use in combination with the partner therapy. As a result, regimens including PD(L)1s are not necessarily cost-ineffective at any price, given the diverse ways in which these treatments can be combined to optimize treatment duration, clinical, and QoL benefits.

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?

Please see response to Question 5.

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.)

Not answered.

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?

Not answered.

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?

<u>Note</u>: Amgen is not currently in first-in-human trials for PD(L)1 inhibitors.

Question 14

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

Not answered.

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 answered.

Question 16
Is there anything else you/your organisation would like to add?