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

Although not currently a sponsor of a PD-1 and PD-L1 checkpoint inhibitor immunotherapy, Takeda Pharmaceuticals Australia (Takeda) welcomes the opportunity to provide some comments for consideration by the Pharmaceutical Benefits Advisory Committee (PBAC) at their Special Meeting in August 2018 in regard to the PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types.

As the sponsor of brentuximab vedotin, an antibody-drug conjugate (ADC) targeted medicine that is also used across several tumour types that express the cell antigen CD30, Takeda is supportive of the need to create a framework for the subsidy of medicines that treat multiple cancer types. However, as brentuximab vedotin is not a PD-1 or PD-L1 checkpoint inhibitor, Takeda is unable to provide answers to the questions specific to the PD-1 and PD-L1 medicines contained in this submission template. Rather, Takeda takes the opportunity to provide a broader statement and to make some suggestions in regard to the topic of enabling access to pan-tumour medicines in a timely and affordable manner in circumstances which do not fit with the current process for listing medicines on Australia's Pharmaceutical Benefits Schedule (PBS). For those questions not specific to the PD-1 and PD-L1 medicines, Takeda also provides some brief comments.

Takeda is concerned that the scope of this particular consideration has been limited to the PD-1 and PD-L1 checkpoint inhibitors, particularly when consideration is given to the following:

- There are several other classes of targeted medicines that treat multiple cancer types, of which Takeda's ADC medicine brentuximab vedotin is one example;
- These other classes of medicines may provide a therapeutic alternative to PD-1/PD-L1s, or be used in combinations with the PD-1/PD-L1s;
- These other classes also represent a significant development in the treatment of oncology; and
- They face the same obstacles to achieving subsidised access, i.e., a listing on the PBS, as those of the checkpoint inhibitors in relation to rare cancers.

Takeda appreciates the difficulties involved in trying to adapt the well-established Health Technology Assessment (HTA) process in Australia to meet the challenges posed by these new targeted medicines and notes that any change may need to be incremental. With this in mind, it views the PBAC's consideration of the subsidy options for PD-1 and PD-L1 medicines as a first step, or pilot; the outcomes from which may then be applied more broadly to other medicines that treat multi-cancer types, as well as to other disease areas where there is a high clinical need and, in which, it is not possible to meet current evidentiary standards to request the listing of a medicine on the PBS.

Takeda also notes:

- Any potential framework for subsidy that results from this review should be viewed as a pilot, the implementation of which should involve sponsors of medicines that include all relevant disease areas, not just those that have a PD-1 or PD-L1 medicine. The involvement of sponsors for the other classes of medicines will ensure that the implications of any changes are thought through from a broader perspective and provide a greater breadth of understanding beyond just the sponsors for this specific group of checkpoint inhibitor medicines. This broad involvement at the beginning (to help develop and finalise the process change) means that it could be subsequently applied on a broader level to the system for reimbursement in Australia, if suitable to do so.
- Any pilot involving the PD-1 and PD-L1 products requires a level of transparency, i.e., any / all changes in the process for reimbursement of / access to these medicines should be made known to other sponsors who do not have these medicines. Transparency is also required as to how, and when, it will apply to other medicines for multiple cancer types specifically; and, importantly, how the PBAC submission process will continue for these other medicines in the absence of a specific pathway alternative. Takeda holds strong concerns about potential equity issues if one class of medicines is to be afforded the option to be part of an expedited process, and not others. Notably, the potential for inequity in timely and affordable access affects all disease areas, not just oncology.
- Consideration needs to be given to the implications of changes (that result from this pilot) on how treatment options that involve the use of other targeted medicines in combination with a PD-1 or PD-L1 checkpoint inhibitor immunotherapy will gain subsidised access in the future. Such consideration involves both the level of evidence required and pricing of these combinations. Although not unique to Australia, the difficulty of gaining reimbursement

via the current HTA process for high cost drug combinations in oncology, for example in multiple myeloma, is already problematic. There are a large number of trials currently underway which are investigating a PD-1 or PD-L1 checkpoint inhibitor, in combination with other classes. Thus, how the reimbursement process will operate for the medicines that are used in combination must be explored and transparent at the time of the pilot.

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?

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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?

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Question 3

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

Takeda considers the question of '*what is urgent unmet clinical need'* is best answered by the patients, their carers / families / communities and the clinicians who treat them.

Takeda believes Australia is in the fortunate position of a having a very well informed / experienced medical community with world class expertise, across all disease areas, especially oncology. As such, the clinicians would be able to provide input on this question, perhaps via an initiative such as the current 'horizon scanning' meetings that take place annually between the PBAC and the specialist clinical organisations, or via input from the specialist organisations with the necessary expertise in that particular cancer – this is especially relevant for the very rare cancers where only a handful of Australian clinicians may have the required knowledge to provide informed input.

Of note in recent years has been the greater involvement of the patients and their communities in the current PBAC process. It is clear their input has been regarded as valuable by the PBAC. This needs to continue and Takeda suggests it could be further strengthened by the formal implementation of an advisory panel to the PBAC / Department of Health, i.e., a 'Patient Panel'. This panel could be comprised of patient organisations / representatives from key disease areas which have been identified (via horizon scanning) as areas in which the pan-tumour medicines will be used. This panel could seek further input, when / if required, to inform the question of 'unmet / urgent clinical need' in a particular disease type.

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?

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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?

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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?

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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?

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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?

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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.

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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?

To date the PBAC's approach to the assessment of the value of medicines has relied on incremental cost-effectiveness ratios (ICERs), as well as consideration of budget impact. The traditional ICER considers only some aspects of 'value' such as response, survival and quality of life. Of note, the current process frequently misses other important 'value' elements associated with improvements with the newer targeted 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 incremental progress in disease management.

Moreover, the current system is not equipped to adequately deal with the need (for timely and affordable access to new medicines) for patients with rare cancers where clinical trials are challenging to conduct, or even impossible to conduct due to the rarity of the condition. This is an equity issue which must be considered for the future. It may be that sufficient information will never be available to determine cost effectiveness for these cancer types and that the focus should move from the ICER to other factors. The numbers of patients with the very rare cancers are small, hence the difficulties of evidence generation. Perhaps for these particular patients, for whom it has been agreed there is a very high and unmet clinical need, the ICER should be supplanted by considerations of other factors such as budget impact (BI). Indeed, for very rare cancers, the BI is likely to be very modest, especially in reference to the more usual cancers with high patient numbers. The certainty of budget impact could be captured via an agreed mechanism, which links outcomes to on-going access and defines (up-front) the expenditure.

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.)

Takeda does not agree with the setting aside of 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. Not only would this result in a reduction in submission opportunities for other medicines (from three times per year to two times), but it has the potential to introduce delays for access to these other medicines, i.e., it would have a negative impact on timeliness for access. This is not an optimal situation for any of the various stakeholders, including the patients, their clinicians, and the sponsors of these other medicines. Moreover, such an approach has the potential to introduce inequity into the system for other medicines across all therapy areas, including other medicines used in oncology that are not a PD-1 or PD-L1 checkpoint inhibitor.

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?

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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?

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Question 14

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

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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?

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Question 16

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

Takeda welcomes the vision of the Government and the PBAC in exploring new approaches to enable timely and affordable access to the targeted medicines, and their commitment to consider how this can be achieved. As the sponsor of a targeted medicine for several very rare cancers (but outside the scope of this meeting), Takeda also appreciates the opportunity to provide input and looks forward to on-going involvement from all stakeholders in this review.