29 June 2018

Pharmaceutical Benefits Advisory Committee
PBAC Secretariat – MDP 952
Department of Health and Ageing
GPO Box 9848
Canberra ACT 2601

RE: PBAC PD-1 and PD-L1 checkpoint inhibitors for the treatment of multiple cancer indications

Dear PBAC,

SHPA is the national professional organisation for over 5,000 pharmacists, pharmacists in training, pharmacy technicians and associates working across Australia's health system. SHPA is the only professional pharmacy organisation with a strong base of members practising in public and private hospitals and other health service facilities. The SHPA Speciality Practice model incorporates an Oncology and Haematology stream which includes members with expertise and practising in oncology and haematology. Members of this stream have informed this submission.

SHPA is committed to facilitating the safe and effective use of medicines, which is the core business of pharmacists, especially in hospitals. SHPA believes that the use of the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings should be driven and underpinned by the principles of consumer safety, evidence-based medicine and quality use of medicines. SHPA has the following remarks with respect to the options for listing PD-1 and PD-L1 checkpoint inhibitors for the treatment of multiple cancer indications on the PBS.

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?

Listing of PD-1 and PD-L1 checkpoint inhibitors for multi-tumour indications will facilitate the availability of therapies in instances where patients have no other satisfactory alternatives. Access to these medicines has the potential to improve patient's quality of life. Listing of the checkpoint inhibitors has the potential to streamline the current application process to access inhibitors. This offers the benefit of reducing redundancies and promoting early access to such important medicines.

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

A potential consequence of listing the PD-1 and PD-L1 checkpoint inhibitors is indication leakage. This refers to the need to regulate and ensure that patients who truly meet the selection criteria are able to access the treatment, and not those who fall outside the criteria. To ensure that patients who would benefit do get the therapy and minimise leakage, PBAC must ensure that any listing limits use of PD-1 and PD-L1 checkpoint inhibitors for defined indications with consideration of how to diminish inappropriate use outside of the listing.

Question 3: What is urgent unmet clinical need? How should it be established? For which patient groups?

In order to address what the urgent unmet clinical need is, it is imperative to start with defining what is entailed as "Urgent". This could possibly be based on how quickly the diseases/ cancer is progressing. The scope of the urgent unmet clinical need should not be defined by specific cancer types, but rather include the expression of a specific tumour biomarker. This can enhance

understanding around the metabolism of the checkpoint inhibitors, along with drug interactions, efficacy and safety.

The PD-1 and PD-L1 checkpoint inhibitors should only be considered for patients who have progressed through standard prior therapy and who may not have any other satisfactory alternative treatment options. This is due to PD-1 and PD-L1 checkpoint inhibitors not being first-line therapy due to the current research pertaining to its use. It is important to note that although this is the current practice, this could change with new evidence.

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?

SHPA recognises that randomised control trials are not easily carried as some cancer types are rare which can entail a lack of clinical expertise in the area. However, evidence of efficacy is still warranted to ensure an objective response rate to the checkpoint inhibitor so that a progression-free survival is obtained. Single arm evidence should be acceptable in well performed and structured trials. This will allow evidence to inform the appropriate dosing of PD-1 and PD-L1, as manageable toxicity of the medicines in patients is equally important.

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?

This question has a two-fold answer. Extrapolating evidence of effectiveness to different tumours which are similar enough with respect to biomarkers may be possible. Evidence of an appropriate biomarker response should be tested to ensure the efficacy of checkpoint inhibitors. However, extrapolating evidence from late-stage to early-stage is not acceptable. There is evidence of efficacy for standard therapy in early-stage cancer which did not manifest in late-stage cancer[1]. Robust evidence is required to test the efficacy of the inhibitors in both early and late-stage cancers.

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?**

See previous responses to Question 3 and 4. Grouping of a tumour will be dependant on how 'different' the tumour types that are being considered behave. Economic models for various tumours should be explored and then assessed if comparable.

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?

SHPA believes that the checkpoint inhibitors should be made available to all patients whose cancers display a particular biomarker. The scope for patients who can access the checkpoint inhibitors should not be defined by specific cancer types but rather include those with the expression of a specific biomarker. PD-1 or PD-L1 expression should not be used as the sole marker for efficacy. While greater expression may result in greater efficacy, patients with poor expression (<1%) have been shown to respond to PD1 or PDL1 therapy. Evidence suggests expression of biomarkers for MSI-H (High Microsatellite Instable) or dMMR (deficit mismatch repair) show response to PD-1 and PD-L1 inhibitors[2].

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.

Evidence from one PD-1 or PD-L1 checkpoint inhibitor should not be extrapolated to other medicines in the same class. These agents are not biosimilars, therefore, there is no guarantee for similar therapeutic outcomes on patients. Substitution across PD-1 with PD-L1 still remains to be seen if a patient gains any therapeutic benefit. In this scenario, they are interchangeable and show no benefit until evidence shows otherwise.

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?

SHPA believes that different evidentiary requirements would be appropriate for the tumour due to their rarity. This means that other study types should be considered other than randomised control trial as mentioned in question 4, so that cost-effectiveness can be attained.

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 PBAC plays a key role in the subsidy of all medicines. While the approval process is slow, foregoing one entire meeting for checkpoint inhibitors would forsake advances in other diseases, which may include cancer, making it inappropriate. A PBAC wide strategy to facilitate a timely review of inhibitors and decision making would be most appropriate.

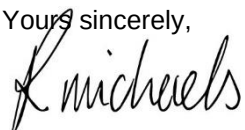
Question 12: If limited evidence is available at the time of subsidy of a PD-1 or PD-L1 inhibitor for a type of cancer, what do you/your organisation think should happen afterwards?

- **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?**

SHPA believes that if there is limited evidence at the time of subsidy, sponsors should fund post-marketing surveillance programme to ensure appropriate use and efficacy of the medicines. Instances where evidence shoes decreased efficacy or increase safety risks, there should be an immediate review of the use of the checkpoint inhibitor in the specific tumour type. Where greater harm to the public is evident, consideration must be given to ceasing funding. The sponsor should not be compelled to make the medicines available even if the price is too low.

If you have any queries or would like to discuss our submission further, please do not hesitate to contact Johanna de Wever, General Manager, Advocacy and Leadership on jdewever@shpa.org.au.

Yours sincerely,



Kristin Michaels
Chief Executive Officer

[1] Dvortsin, E., Gout-Zwart, J., Eijssen, E.-L. M., van Brussel, J., & Postma, M. J. (2016). Comparative Cost-Effectiveness of Drugs in Early versus Late Stages of Cancer; Review of the Literature and a Case Study in Breast Cancer. *PloS One, 11*(1), e0146551. doi:10.1371/journal.pone.0146551

[2] Yamashita, H., Nakayama, K., Ishikawa, M., Nakamura, K., Ishibashi, T., Sanuki, K., Kyo, S. (2018). Microsatellite instability is a biomarker for immune checkpoint inhibitors in endometrial cancer. *Oncotarget*, *9*(5), 5652–5664. http://doi.org/10.18632/oncotarget.23790