28th June 2018

Professor Andrew Wilson
Chair, Pharmaceutical Benefits Advisory Committee
Department of Health
Canberra ACT 2600

cc. pbac@health.gov.au

Dear Professor Wilson,

Re: PBAC special meeting regarding PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types.

We welcome the Pharmaceutical Benefits Advisory Committee's convening of a special meeting to consider these issues and the opportunity to provide input. As Australia's largest non-government cancer control organisation, Cancer Council has a high stake in ensuring equitable access to cancer medicines to Australians who need them.

Cancer is increasingly classified based on the genetic profile of the tumour, rather than its location. This has shifted treatment discovery towards therapies that target specific abnormalities that drive tumour growth. Identifying the specific biomarker is critical in the accuracy of targeting and in predicting response. In the case of epidermal growth factor receptor (EGFR) inhibitors, original lung cancer trials did not show a response differential between positive and negative tumours. However, further investigation of an enabling abnormality subsequently improved the accuracy of the response prediction.

This submission focuses on the critical distinction between publicly funded access to PD-1 and PD-L1 checkpoint inhibitor immunotherapies for cancers where there is clear evidence of effectiveness, and for use in situations when all other treatment options have been exhausted or where no treatment options exist.

As a general point, Cancer Council Australia strongly supports measures to expedite access to new medicines for patients who may benefit. Patients with poor prognoses, can understandably be desperate to access new medicines, even when the evidence of benefit is unclear. This should not always be taken to imply Governments should fund such access. We offer some key principles that might guide the committee's deliberations.

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Principle one: The ability for pan-tumour approvals has merit when considering cancers with small patient numbers where conducting traditional clinical trials is not feasible to establish efficacy.

The impact of the drug on its target can be demonstrated through application in clinical trials for common cancers. This may be sufficient to allow use in cases with the same target where only evidence through case reports from a small series of patients is available.

We appreciate that a consistent and rigorous approach to assessments must occur, even after safety and potential efficacy have been considered – primarily because the costs to the health system can be extraordinarily high and with those costs comes a risk that federal funds could be diverted from other programs that provide greater benefit and more equitable overall cancer outcomes. This problem, in our view, is the result of the pricing policies of the drug companies – and is the major barrier to more flexible and innovative options for expediting access. Therefore, as well as supporting measures to expedite access to medicines for people who need them, we would also support collaborative measures to put more pressure on industry to support more flexible equitable pricing policies.

Principle two: To promote efficient use of medicines, targeted therapies and immunotherapies should only be used after measuring for and ascertaining the presence of the corresponding target.

The discovery of PD-1 and PD-L1 checkpoint inhibitors has significantly changed the understanding of cancer, and the approach to treatment. To date, effectiveness studies indicate a highly variable relationship between the target cohort and the patients who go on to experience a positive result. This variability is also seen across different cancer types. Current predictive markers of response do not consistently result in positive outcomes, and this uncertainty impacts the ability to assign a broad cost-effectiveness assessment to the use of PD-1 and PD-L1 checkpoint inhibitor immunotherapies.

Internationally, Keytruda is approved for a range of indications as both monotherapy, and in combination with chemotherapy, as first line treatment or a subsequent treatment option. Most indications are for advanced disease, and the eligibility for use is extensive, including the presentation of tumour expression PD-L1 at a certain concentration. Improvements in overall survival, progression-free survival or health-related quality of life have not been established in all indications, and the magnitude of the benefit to the individual patient is uncertain. From our understanding of the evidence, the current system for the assessment of applications is flexible enough to individually consider different endpoints and their benefit. However, the assessment of PD-L1 checkpoint inhibitors for multiple indications within a single economic funding model would be challenging. Complex risk sharing arrangements or other mechanisms under the Deeds of Agreement would need to be considered, as well as an expectation that the sponsor is committed to the ongoing investigation of the product's effectiveness.

Pembrolizumab has a consistent response in the treatment of advanced melanoma in eligible patients. The overall response rate to treatment is 42% in patients with positive PD-L1 expression (at least 1% of tumour concentration) while only 9% in PD-L1 negative patients[i]. PD-L1 positive patients experience double the time without disease progression compared to PD-L1 negative patients (24 v. 12 weeks). Similarly, in a PD-L1 positive patient cohort, improvement in progression-free survival at six-months was nearly double, and 12-month overall survival improvement of 16% with pembrolizumab over standard care[ii]. In comparison, the current indication for pembrolizumab for non-small cell lung cancer requires patients to have 50% or more PD-L1 tumour expression. In these patients there is an 8% increase in survival at six months compared to standard care[iii]. Another immunotherapy, Vemurafenib, which targets a mutated form of the protein B-RAF1, reports being effective for 48% of melanomas with the B-RAF1 mutation. While it has been effective in melanoma, only 5% of people with colon cancer and the B-RAF1 mutation respond to the drug[iv]. The reason for variation in response across cancer types that target a particular pathway is not fully understood. A positive classification is currently the best available evidence of a predictive response, and therefore, target status should be measured as part of the treatment decision.

Principle three: Therapeutic pricing should be determined based on the value of a drug, considering efficacy, toxicity and cost.

In our view, the PBS framework seeks to apply an equitable approach to the assessment of cost-effectiveness. For some cancer indications the availability of treatment options is limited, however, introducing a separate process for drugs targeting specific patient groups may be problematic to the fundamental principle of equity. To maintain an equitable approach, affordable access in these circumstances should be provided based on the therapy's potential to address an urgent unmet need. The public subsidy must reach those who most need it and ensure that patients with limited options or where effective treatments have been exhausted, can access potentially effective therapies where there is at least a potential for response. This would maintain a balance between the use of public funding to ensure greatest health benefit for the greatest number of people, and a government's responsibility to look after the most vulnerable.

There is increased demand to improve timely and affordable access to promising treatments for patients. The Therapeutic Goods Administration (TGA) has introduced two new pathways to manage the assessment of quality and safety based on uncertain data for promising treatments that meet an urgent unmet need. These assessments are made based on preliminary or incomplete data. Products are assessed on a per indication basis and must demonstrate a commitment to ongoing data collection with the intention of progressing to full registration. Although this does not account for cost-effectiveness, it does demonstrate the implementation of differing processes based on the level of certainty in the data combined with patient need. We are not aware of a comparable overseas regulator who has approved

a category of therapeutic products, such as PD-1 and PD-L1 checkpoint inhibitor immunotherapies, for public subsidy across multiple indications.

Although not assessed for cost-effectiveness, Keytruda was the first product approved by the United States Food and Drug Administration (FDA) for multiple cancers by biomarker expression. This was assessed through the Accelerated Approval pathway, under which the FDA may approve drugs for serious conditions where there is unmet medical need and a drug is shown to have certain effects that are reasonably likely to predict a clinical benefit to patients.

The Cancer Drugs Fund (CDF) held by the National Health Service (NHS) in the United Kingdom aims to make promising cancer drugs available to patients before they are fully approved for use in the NHS. It is a discrete pool of funding which was introduced as a temporary solution to support clinicians and their patients gain access to cancer drugs not routinely available on the NHS. Although it has provided support to many patients, a lack of clarity for how and when drugs exit the scheme and continue to be accessible through public care has contributed to its unsustainability. The National Institute for Health and Care Excellence (NICE) originally recommended Keytruda for patients with previously untreated metastatic non-squamous non-small cell lung cancer (NSCLC) through CDF funding instead of NHS public funding. However, in early June 2018 a pricing arrangement between the sponsor and NHS England, has meant that Keytruda has been deemed cost-effective for routine commissioning in NHS England. Without clear parameters set for discontinuation of funding or movement of access to the PBS scheme, we would not advocate for a dedicated pool of funds for specific products.

Similarly to the PBAC, the Canadian Agency for Drugs and Technologies in Health (CADTH) conducts thorough and objective evaluations to provide reimbursement recommendations and advice. Keytruda has been recommended for public funding for several indications however, each application received individual assessment.

A Pharmaceutical Benefits Schedule (PBS) listing and the commitment of public funds, is an endorsement for a product's utility and value. The collective assessment of PD-1 checkpoint inhibitor immunotherapies may require a multifaceted approach as a single economic model for pricing may not adequately capture the current variation in effectiveness across specific indications.

Ultimately, these types of innovations would be fairer and more effective if the pharmaceutical industry would compromise more on price when taking patent-protected oncology medicines to the Australian market. We will continue to make this point, although it is out of scope of this consultation. At a base level, we contend that exceptional access schemes should be confined to specialist centres who are compelled to collect trial level outcomes data to assist in longer term evaluation of impact.

Thank you again for the opportunity to comment.

Yours sincerely,

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[redacted]
[redacted] **Cancer Council Australia**

[i] Department of Health, Therapeutic Goods Administration. *Australian Public Assessment Report for Pembrolizumab*, October 2016. Commonwealth Government: Canberra. Accessed on 22nd June 2018 via https://www.tga.gov.au/sites/default/files/auspar-pembrolizumab-rch-161014.pdf

[ii] Robert C, et. al. *Pembrolizumab versus Ipilimumab in Advanced Melanoma*. N Engl J Med 2015;372:2521-32. https://www.nejm.org/doi/full/10.1056/NEJMoa1503093

[iii] Reck M, et. al. *Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small Cell Lung Cancer.* N Engl J Med 2016;375:1823-33 https://www.nejm.org/doi/full/10.1056/NEJMoa1606774

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