PD-(L)1 checkpoint inhibitor stakeholder meeting

08 February 2019

Attendees

All invited stakeholders participated, including members of the Pharmaceutical Benefits Advisory Committee (PBAC), representatives of the Lung foundation (LF), the Medical Oncology Group of Australia (MOGA), AstraZeneca (AZ), Bristol-Myers Squibb (BMS), Merck Sharpe & Dohme (MSD), Roche and the Department of Health. A representative from Medicines Australia (MA) attended, as an industry invitee.

Non-departmental attendees undertook confidentiality declarations and provided conflict of interest statements.

Purpose of meeting

The PBAC Chair Professor Andrew Wilson outlined the goals of the stakeholder meeting as:

- Establishing interest from stakeholders in pursuing a potential broad non-small cell lung cancer (NSCLC) listing for PD-(L)1 inhibitors;
- Exploring a potential model for a broad NSCLC listing for PD-(L)1 inhibitors;
- Discussing stakeholder issues surrounding a potential broad NCSLC listing; and
- Exploring the potential for this model to be applied in alternate contexts.

Background

In late 2017 the Hon. Greg Hunt MP, Minister for Health, requested the PBAC provide advice on options for listing PD-1 and PD-L1 (PD-(L)1) inhibitors for the treatment of multiple cancer indications on the Pharmaceutical Benefits Scheme (PBS). Specifically, the Minister asked the PBAC to provide advice on:

1) The current status of PD-(L)1 inhibitors for the treatment of cancer;

2) Any issues around access to medicines for people with rare cancers, particularly where there are no existing effective therapies; and

3) Options that could broaden or lead to faster PBS listing for cancer indications.

The PBAC elected to publish its initial views on this topic through a discussion paper in May 2018 and sought input from interested stakeholders ahead of further consideration at its August 2018 and November 2018 meetings. The PBAC provided its final advice to the Minister in December 2018. Publication of the report on the PBS website is subject to the Minister's consideration.

The PBAC has considered 13 submissions for PD-(L)1 inhibitors for use in NSCLC in a variety of patient populations and lines of therapy to date (as at February 2019). Further submissions are anticipated (Table 1).

Table 1: TGA and PBAC submissions for PD-(L) 1 inhibitors for NSCLC (Bold text indicates positive PBAC recommendation) as at February 2019

Drug and Indication	TGA submission	TGA approval	PBAC consideration			PBS listing
			First	Second	Third and subsequent	
NIVOLUMAB						
Treatment of locally advanced or metastatic squamous NSCLC with progression on or after prior chemotherapy	[redacted]	11 January 2016	March 2016	November 2016	**March 2017** (combined non-squamous and squamous consideration)	August 2017
Treatment of locally advanced or metastatic non-squamous NSCLC with progression on or after prior chemotherapy.	[redacted]	17 February 2016	March 2016	November 2016	**March 2017** (combined non-squamous and squamous consideration)	August 2017
PEMBROLIZUMAB						
First-line treatment of patients with metastatic NSCLC whose tumours express PD-L1 with a greater than or equal to 50% tumour proportion score (TPS) as determined by a validated test, with no EGFR or ALK genomic tumour aberrations	2016	3 March 2017	March 2017	November 2017	March 2018 **July 2018**	November 2018
In combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic non-squamous NSCLC	2017	8 June 2018	November 2018			
Treatment of patients with advanced NSCLC whose tumours express PD-L1 with a greater than or equal to 1% TPS as determined by a validated test and who have received platinum-containing chemotherapy.	2016	3 March 2017	November 2016			
ATEZOLIZUMAB						
Locally advanced or metastatic NSCLC with progression on or after prior chemotherapy.	2016	26 July 2017	**November 2017**			April 2018
In combination with paclitaxel and carboplatin, with or without bevacizumab, for the first-line treatment of patients with metastatic non-squamous NSCLC	[redacted]		March 2019			
DURVALUMAB						
Treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy.	2017	22 October 2018	November 2018			

A summary of the patient number estimates for NSCLC in Australia, based on assumptions previously accepted by the PBAC is provided in Table 2.

Table 2: NSCLC patient population eligible for treatment with PD-(L)1 inhibitor

		2018	2019	2020	2021	2022	2023	2024	
New cases of lung cancer		12509	12750	12990	13230	13470	13711	13951	Forecasted from AIHW incidence data.
Proportion of lung cancer that is NSCLC	86.6%	10833	11041	11249	11457	11665	11873	12082	"Lung cancer in Australia: an overview" (AIHW 2011). Source previously accepted by PBAC
Stage for NSCLC									Mitchell et al. (2013). Source previously accepted by PBAC.
III	25.8%	2795	2849	2902	2956	3010	3063	3117	
IIIA	11.8%	1278	1303	1327	1352	1377	1401	1426	
IIIB	14.0%	1517	1546	1575	1604	1633	1662	1691	
IV	51.5%	5579	5686	5793	5900	6008	6115	6222	
Total Stage III/IV		8374	8535	8696	8856	9017	9178	9339	
ECOG performance status score for NSCLC									Mitchell et al. (2013). Source previously accepted by PBAC.
0-1	63.3%	5301	5402	5504	5606	5708	5810	5912	
Proportion opting for treatment									
	85%	4506	4592	4679	4765	4852	4938	5025	Assumption, previously accepted by PBAC

ECOG= Eastern Cooperative Oncology Group

At the November 2018 PBAC meeting, the Committee noted the likelihood of further PD-(L)1 inhibitor submissions for NSCLC, and agreed to advise the Minister to examine the potential for a broad PBS subsidy listing for PD-(L)1 checkpoint inhibitors in NSCLC. The PBAC noted that substantial evidence and experience is now available for four PD-(L)1 medicines in this setting. A broad listing would allow patients with NSCLC of WHO performance status 0 and 1, access to a single course of treatment with a PD-(L)1 inhibitor, irrespective of disease stage (unresectable stage III or IV), biomarker status, line of treatment (adjuvant, 1st or later line), and with or without concomitant cytotoxic therapy.

In providing its advice, the PBAC noted that a broad listing had the potential to:

- Allow clinicians and patients to make their own decisions regarding best treatment;
- Simplify administrative burden;
- Rapidly accommodate advances in treatment practice; and
- Support innovation and competition.

The PBAC also noted the need to achieve a price per patient and overall cost to government, which is justified by the currently available evidence. The PBAC recommended overall financial caps be put in place to manage the risks associated with a broad listing approach, in particular the risk that patients will be treated with sequential courses of PD-(L)1 therapy, for which no evidence has yet been put to PBAC.

Summary of discussion

Overall, stakeholders expressed an interest in exploring the development of a broad NSCLC listing for PD-(L)1 inhibitors. During the meeting, stakeholders identified several key issues and challenges surrounding the progression of a broad NSCLC listing.

The Minister's original request

Some of the pharmaceutical industry attendees considered a broad NSCLC listing for all eligible PD-(L)1 inhibitors deviates from their understanding of the Minister's request to the PBAC. This was viewed by those stakeholders as a missed opportunity to provide a way forward for listing PD-(L)1 inhibitors across several tumour types.

At the November 2018 meeting, the PBAC recommended exploring a potential broad NSCLC subsidy listing given the number of submissions, as well as the substantial evidence and experience now available for four PD-(L)1 medicines in this setting. Exploring a broad NSCLC listing also provides an opportunity for stakeholders to have a concrete discussion on issues surrounding broad listings, on a smaller scale, and to find solutions for issues that will apply to any broad listing proposal.

The PBAC Chair emphasised that this was but one of several recommendations made by the PBAC to the Minister in its final report, and that PBAC had initiated work on this recommendation in the context of the many recent and upcoming PBS listings submissions for NSCLC. The Chair noted the challenge of a broader multi-tumour listing was the increased level of uncertainty about relative benefits in different cancer types and therefore the ability of the PBAC to meet its legal requirements to ensure cost-effectiveness when recommending drugs for subsidy on the PBS.

Timely access to PD-(L)1 checkpoint inhibitors

Ensuring timely access to PD-(L)1 inhibitors was a priority for all stakeholders. The pharmaceutical industry attendees wanted to ensure that the process of developing a broad NSCLC listing would not delay PD-(L)1 inhibitor submissions currently under consideration by the PBAC. The PBAC Chair assured stakeholders that there will be no changes to the consideration of current or future PD-(L)1 inhibitor submissions as a result of this process. Exploring a broad NSCLC listing for PD-(L)1 inhibitors will be done in parallel to PBAC consideration of sponsor submissions. Sponsors intending to make future PD-(L)1 inhibitor submissions to the PBAC were encouraged to proceed with those submissions as scheduled.

TGA registration and PBS subsidy

There was some discussion surrounding the TGA registration of medicines and PBS subsidy.

A concern raised by one industry sponsor was the possibility that it would not be able to accept reimbursement for a PBS listing which did not correspond directly with its TGA registered indication. Not all industry sponsors shared this concern, with some considering reimbursement was possible under these circumstances.

The PBAC Chair emphasised the PBAC was not advocating prescribing outside of TGA registered indications, but allowing the decision of when and which drug to use in the course of the disease to be at the discretion of the clinician and patient.

The PBAC considers a broad lung listing for PD-(L)1 inhibitors is not a move away from the PBAC's general approach, where subsidy is restricted to particular patient groups through "restricted benefit" or "authority required" listings. The PBAC considers that NSCLC is an indication where there is now a substantial body of evidence for PD-(L)1 inhibitors making it suitable for exploring in a concrete way, the potential for a broad or "pan" listing and that such an approach need not be inconsistent with TGA registration/processes. PBS listings do not remove the prescribing doctor's obligations to be cognisant of TGA registered indications.

PD-(L)1 inhibitors overlap in their current or proposed NSCLC subsidised indications (Figure 1), therefore providing access to several PD-(L)1 inhibitors in a broad listing setting aims to promote flexibility for clinicians and patients, allowing them to make their own decisions regarding best treatment.

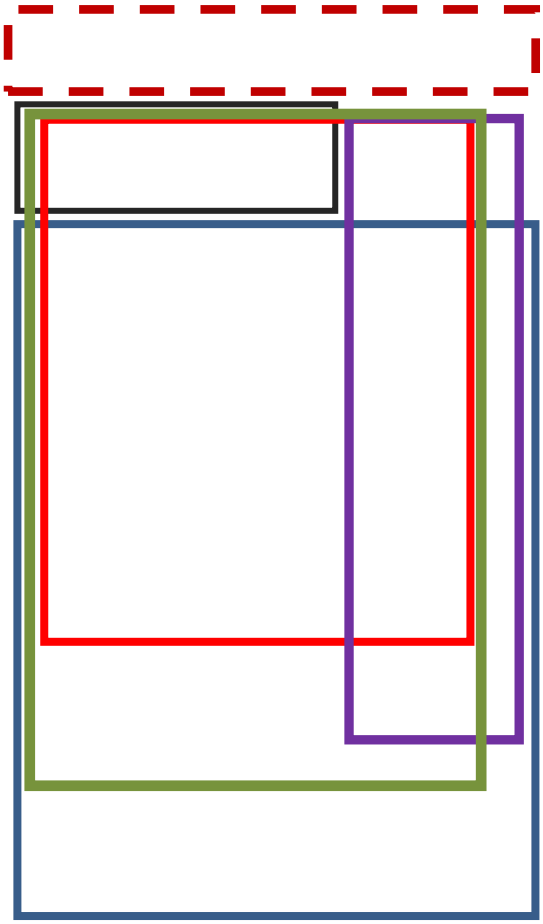

Figure 1: (conceptual representation and not to scale): NSCLC population targeted across the 14 PD-L(1) inhibitor submissions received by the PBAC (as at March 2019)

The clinical experts from MOGA considered that the prescribing choices made by oncologists are based on the clinical evidence available with regard to the appropriate treatment-line and disease stage and would remain so within the context of a broad listing. The consumer representatives had some concerns that a broad PBS listing might result in variations in health care due to location, prescriber, or patient knowledge.

The PBAC Chair clarified that consistent with the PBAC's advice at the time of recommendation, under subsection 101 (3A) of the *National Health Act 1953*, none of the three PBS-listed PD-(L)1 inhibitors indicated for NSCLC, are considered interchangeable on an individual patient basis with any other PD-(L)1 drugs .

Limiting access to once per lifetime

A common challenge for a broad listing raised by stakeholders was the proposed 'once in a lifetime' restriction.

All stakeholders acknowledged that a once in a life-time restriction is currently applied to PD-(L)1 inhibitor subsidy for NSCLC and is a result of a lack of evidence around re-initiation of PD-(L)1 treatment in recurrent disease.

All stakeholders expressed concerns with the inability for clinicians to prescribe PBS-subsidised retreatment with a PD-(L)1 inhibitor, particularly on occasions where a patient was successfully treated with a PD-(L)1 inhibitor and has experienced an extended period without disease progression, or has been successfully treated for Stage III disease and then presents with Stage IV disease. The clinical and patient representatives were particularly concerned that the 'once in a lifetime' restriction places significant barriers on the effective management of patients, including placing undue stress on the prescriber and the patient to optimally time the use of a PD-(L)1 inhibitor in the treatment regimen.

The clinical experts from MOGA made the further recommendation that stage III NSCLC and stage IV NSCLC should be considered separate clinical entities. MOGA's view is that treatment has the potential to be curative in a proportion of stage III patients as opposed to stage IV which is considered incurable. The MOGA clinicians considered that if a broad lung listing does move forward, these two NSCLC stages should not be grouped together. If a broad listing encompassing both stages does proceed, the MOGA representatives were of the opinion that clinicians would be concerned if a limit on retreatment was applied (e.g. patients are only able to be re-treated if they relapse beyond a certain timeframe). The MOGA clinicians present did not consider applying a limit on retreatment was appropriate in this instance, considering the absence of evidence of effect also means there is no evidence available to guide retreatment, therefore the decision should be left to the treating clinician and patient. The MOGA representatives considered a limit on retreatment would lead to complexity and confusion, with the potential to deny patients active therapy.

The clinicians present also expressed that the 'once in a lifetime' restriction disadvantages patients who are responding well to immunotherapy and are suitable candidates for a treatment break. This could lead to a situation where clinicians continue treating these patients to avoid the current prohibition on the re-initiation of treatment with a PD-(L)1 inhibitor.

Sequential treatment with PD-(L)1 inhibitors in patients unresponsive to previous PD-(L)1 inhibitor treatment was also discussed. In this instance, the clinicians present were not in favour of relaxing the current 'once in a life time' restriction, due to a lack of evidence.

The PBAC members were sympathetic to the issues arising from maintaining the 'once in a lifetime' restriction. The Committee members made a commitment to look at mechanisms for dealing with shorter treatment breaks.

All attendees acknowledged that if evidence were to emerge indicating that sequential treatment of PD-(L)1 inhibitors in NSCLC was effective and cost-effective, then the PBAC would reconsider this restriction. Alternatively, sequential treatment could be facilitated through pricing and financial mechanisms.

Consideration of new evidence

There were a number of concerns raised relating to the ability for a broad listing to evolve as new clinical evidence becomes available. Attendees wanted to ensure that if a broad NSCLC listing was to be implemented, any new evidence relating to new treatments or variations to current treatments would be incorporated. This included new evidence related to biomarkers.

The PBAC Chair confirmed as is currently the case, if new evidence becomes available, sponsors are able to make submissions to the PBAC for consideration of amendments to the conditions of subsidy. Any new PD-(L)1 inhibitor treatments that become available would be eligible for inclusion in the broad NSCLC listing. New evidence in the combination setting, or in relation to biomarkers can also be considered as it becomes available and appropriately accounted for in a broad NSCLC listing.

Next Steps

The PBAC Chair thanked participants for their time in attending the stakeholder meeting and for their interest in working collaboratively on the potential broad listing for PD-(L)1 inhibitors. The PBAC Chair considered the meeting had usefully identified a range of issues associated with a broad listing but none precluded further consideration of options for a broader listing. It was also noted that most of the issues identified in relation to a broad listing for NSCLC would also apply to any future multi-tumour listings.

The Chair proposed that sponsors confirm their interest in progressing this matter within a fortnight of the meeting and, if there is sufficient interest, a closing date for proposals would be provided to sponsors following the stakeholder meeting. The Chair noted it is open to sponsors to make new listing proposals to PBAC at any time, irrespective of this process.