Agenda item 11.05
Broad PBS subsidy listing for PD-(L)1 checkpoint inhibitors for non-small cell lung cancer

1 Purpose of Item

1.1 To consider proposals for an approach to a broad PBS subsidy listing for PD-L1 and PD-1 (collectively referred to as PD-(L)1) checkpoint inhibitors for non-small cell lung cancer (NSCLC).

2 Background

2.1 Previous PBAC advice to the Minister on PD-(L)1 inhibitors[1] (December 2018) recommended the Minister request additional advice on (paragraph 4.3):

- Options for a broad PBS subsidy listing for PD-(L)1 inhibitors for lung cancer, as substantial evidence and experience is now available for these medicines in this setting.
- Options for a standardised tiered pricing arrangement for PD-(L)1 inhibitors that would apply once the PBAC has recommended subsidy for a particular use and that would account for issues beyond PBAC's scope including economies of scale and affordability considerations.

2.2 Following this advice to the Minister, a stakeholder meeting was held on 8 February 2019 to discuss the potential for a broad PBS subsidy listing for PD-(L)1 inhibitors for NSCLC. Stakeholders included members of the PBAC, representatives of the Lung Foundation, the Medical Oncology Group of Australia, Department of Health, Medicines Australia and the sponsors of the PD-(L)1 inhibitors that are currently TGA approved for the treatment of NSCLC (AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme and Roche).

2.3 The purpose of the stakeholder meeting was to: (i) establish the interest from stakeholders in pursuing a potential broad NSCLC listing for PD-(L)1 inhibitors; (ii) explore a potential model for a broad NSCLC listing; (iii) discuss stakeholder issues surrounding a broad NSCLC listing; and (iv) explore the potential for this model to be applied in alternate contexts. An outcome statement for the meeting has been published[2].

[1] http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/agenda/pdf/august-2018-special-meeting/pbac-pdl1-report-to-minister.pdf
[2] http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-stakeholder-meetings/pdl1-

2.4 Based on the interest expressed at the stakeholder meeting, on the 25 February 2019, sponsors were invited to submit proposals for an approach to a broad lung listing for consideration by the PBAC. Sponsors were given an opportunity to individually meet with representatives of the Department of Health in early March and proposals were required by 29 March 2019.

3 Summary of the proposals

3.1 Proposals were received from the four sponsors that attended the stakeholder meeting and their proposals are briefly discussed below.

Roche Products Pty Ltd for atezolizumab (Tecentriq®)

[redacted]

stakeholder-%20meeting-outcome-statement.pdf

AstraZeneca Pty Ltd for durvalumab (Imfinzi™)

[redacted]

Bristol-Myers Squibb Australia Pty Ltd for nivolumab (Opdivo®)

[redacted]

Merck Sharp & Dohme (Australia) Pty Ltd for pembrolizumab (Keytruda®)

[redacted]

4 PBAC consideration

4.1 A summary of the approved TGA indications and PBS listing status of PD-(L)1 inhibitors is provided in Table 1. The PBAC noted that for similar patient populations there were differences in the TGA indications for the PD-(L)1 inhibitors with some medicines indicated as monotherapy treatments, some in combination with chemotherapy, some were limited by PD-L1 TPS status and some were limited to patients without targeted mutations.

Table 1: TGA indications (PBS listing status)

	Durvalumab	Nivolumab	Atezolizumab	Pembrolizumab
Stage III post CRT	✓ (rejected)[1]	✖	✖	✖
Stage IV, first-line NSQ	✖	✖	✓ (recommended)	✓ (recommended)
Stage IV, first-line SQ	✖	✖	✖	✓ (PD-L1 TPS ≥ 50% listed)
Stage IV, second-line NSQ	✖	✓ (listed)	✓ (listed)	✓ (rejected)
Stage IV, second-line SQ	✖	✓ (listed)	✓ (listed)	✓ (rejected)

1. Rejected at November 2018, July 2019 PBAC meeting. On agenda for consideration at November 2019 PBAC meeting.

NSQ=non-squamous, SQ=squamous, PD-L1 = programmed death-ligand 1, TPS= tumour proportion score

4.2 The PBAC noted a number of the PD-(L)1 inhibitors demonstrated an overall survival benefit for the treatment of NSCLC. However the available clinical data varied substantially by line of therapy (first-line, second-line), disease stage (Stage III, Stage IV), histology (SQ, NSQ), targeted mutation status, PD-L1 TPS status and chemotherapy backbone. The PBAC further noted that for some medicines there was an absence of data and for some medicines there was evidence that did not support use (no overall survival benefit) or that was negative (evidence of harm). However, the PBAC also noted that some studies may be considered 'false negatives' (i.e., not adequately powered to show a benefit, confounded or due to chance).

4.3 The PBAC noted that since March 2016 it had considered numerous submissions for NSCLC including several in parallel with its broad lung listing considerations. The PBAC noted listings or recommendations were in place for most patients with Stage IV NSCLC. The PBAC noted the only patient cohort with Stage IV disease and without targetable mutations that did not currently have access to first-line treatment with a PD-(L)1 inhibitor were patients with SQ histology and PD-L1 TPS <50%.

4.4 The PBAC noted that it had rejected two submissions for durvalumab for the treatment of Stage III unresectable NSCLC in patients who have not progressed after platinum-based chemoradiation therapy (consolidation treatment). At its most recent consideration (July 2019) the PBAC considered the incremental cost effectiveness ratio was high and potentially underestimated. The PBAC also considered the total cost of subsidising durvalumab in this setting to be very high and uncertain. The PBAC noted durvalumab was included on the agenda for consideration at the November 2019 PBAC meeting.

4.5 The PBAC considered each of the sponsor proposals and noted that there are numerous clinical studies underway for all the PD-(L)1 inhibitors across a range of patient populations and there was a consistency across the proposals that use be guided by the approved TGA indications for each PD-(L)1 inhibitor.

5 PBAC Outcome

5.1 The PBAC decided not to recommend a broad PBS listing for the PD-(L)1 inhibitors at this time. In making this recommendation the PBAC took into account the varying clinical evidence for each PD-(L)1 inhibitor, its inability to make a recommendation that encompasses use in the Stage III setting and the absence of a compelling financial offer from any sponsor. Furthermore, the PBAC noted that the current listings, or recommended listings, provide PD-(L)1 inhibitor access to the majority of people with Stage IV NSCLC.

5.2 As part of its consideration of the sponsor proposals, the PBAC noted the KN-407 data provided evidence of an overall survival benefit for patients with previously untreated Stage IV SQ NSCLC. The PBAC considered it would be appropriate for pembrolizumab to be available for this patient population on the basis of a high clinical need and to ensure PD-(L)1 inhibitors were available for all patients with Stage IV NSCLC as first line therapy. The PBAC was satisfied that pembrolizumab provides, for some patients, a significant improvement in efficacy over alternative treatments. [redacted]

5.3 The PBAC considered the listing for pembrolizumab could be consolidated and recommended a listing of pembrolizumab for previously untreated Stage IV NSCLC without targetable mutations. The PBAC considered it would be reasonable for clinicians to determine whether pembrolizumab was used in combination with chemotherapy or as monotherapy according to its approved TGA indications.

5.4 The PBAC recommended treatment with a PD-(L)1 inhibitor for NSCLC should be limited to one course per lifetime until there is adequate clinical and economic evidence available to support retreatment. The PBAC recalled it had previously advised that the current restrictions for first-line and second-line treatment of Stage IV NSCLC included sufficient provisions to ensure that the PBS does not subsidise sequential immunotherapy for NSCLC (paragraph 6.10, pembrolizumab PSD, July 2018 PBAC meeting). The PBAC previously noted that should any PD-(L)1 inhibitors be listed in an earlier disease stage, additional restriction wording for all PD-(L)1 inhibitors may be warranted (paragraph 6.10, pembrolizumab PSD, July 2018 PBAC meeting). The PBAC noted that retreatment may be more likely to be considered clinically appropriate if PD-(L)1 inhibitors are used earlier in the treatment algorithm (i.e., consolidation or adjuvant setting).

5.5 The PBAC noted that the recommendation to list pembrolizumab on the PBS for patients with previously untreated Stage IV NSCLC without targetable mutations was made in the context of a referral from the Minister for advice.

6 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

7 Sponsor's Comment

Roche Products Pty Ltd

The sponsor had no comment.

AstraZeneca Pty Ltd

The sponsor had no comment.

Bristol-Myers Squibb Australia Pty Ltd

BMSA applauded the Minister for Health's request that the PBAC explore options for listing PD-1 and PD-L1 checkpoint inhibitors for the treatment of multiple cancer indications on the PBS. BMSA has, and will continue to work with the PBAC to explore options that deliver timely access to these innovative medicines for Australian patients.

Merck Sharp & Dohme (Australia) Pty Ltd

MSD welcomes the PBAC's decision for a consolidated listing of pembrolizumab for the treatment of 1L Stage IV NSCLC patients ensuring equity of access across different patient sub-groups, where there is evidence of efficacy. MSD supports the use of similar pragmatic access approaches in the future where there is a high clinical need in new and emerging treatment areas.