Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1440 – PDL1 testing for access to pembrolizumab in treatment naïve patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)

Applicant: **Merck, Sharpe & Dohme**

Date of MSAC consideration: **MSAC 69th Meeting, 6-7 April 2017**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

The co-dependent application requested:

- Medicare Benefits Schedule (MBS) listing of immunohistochemistry (IHC) testing for the evaluation of programmed cell death ligand 1 (PD-L1) expression in treatment-naïve patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) and who do not have an activating epidermal growth factor receptor (*EGFR*) gene mutation or an anaplastic lymphoma kinase (*ALK*) gene rearrangement in tumour material*; and*
- Section 100 (Efficient Funding of Chemotherapy) Authority Required Pharmaceutical Benefits Scheme (PBS) listing for first-line treatment with pembrolizumab of those patients whose IHC results show evidence of high levels of expression of PD-L1, defined as a tumour proportion score (TPS) of ≥50%.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC did not support public funding of programmed death ligand 1 (PD-L1) immunohistochemistry (IHC) as a companion diagnostic test for selecting patients with non-small cell lung cancer (NSCLC) for treatment with pembrolizumab.

MSAC considered that PD-L1 IHC is a poor companion diagnostic test with insufficient evidence of analytical and clinical validity, and clinical utility. MSAC advised that, as PD-L1 is an imperfect biomarker, there is a likelihood that patients who might benefit from pembrolizumab treatment would be excluded by the test result.

MSAC recommended that any resubmission would need to be considered by ESC.

3. Summary of consideration and rationale for MSAC's advice

The application to list PD-L1 IHC testing in the MBS was part of an integrated codependent submission, which also requested that PBAC consider listing of pembrolizumab in the PBS for the first-line treatment of locally advanced or metastatic NSCLC. The proposed PBS criteria included a requirement that the patient must have high expression of PD-L1 — defined as a tumour proportion score (TPS) ≥50% — and no evidence of an activating epidermal growth factor receptor (*EGFR*) gene mutation or an anaplastic lymphoma kinase (*ALK*) gene rearrangement.

NSCLC accounts for the approximately 85% of all lung cancer cases. The development of agents targeting specific genetic mutations (*EGFR* mutation and *ALK* gene rearrangement) has led to improved outcomes for some NSCLC patients. However, the majority of NSCLC patients (80–85%) have no identifiable genetic mutation which can be targeted with drug therapy and thus until recently have no option other than untargeted chemotherapy.

Pembrolizumab belongs to a new class of immunotherapy which targets the PD-1 pathway and may help these patients. PD-L1 is preferentially expressed on the surface of NSCLC tumour cells and binds to PD-1 receptors on T-cells to switch off the immune response. Antibodies that bind to PD-1 on the T-cells (e.g. pembrolizumab and nivolumab) disrupt this pathway, allowing T-cells to recognise the tumour cells and initiate activated death of the tumour cell. The rationale for testing levels of PD-L1 expression is that it may predict variation in the extent of clinical response to pembrolizumab treatment.

MSAC noted that the proposed clinical algorithm indicated that PD-L1 IHC would be an additional test undertaken at the diagnosis of advanced NSCLC on a biopsy sample where prior *EGFR* and *ALK* testing had already determined ineligibility for other existing targeted treatments.

MSAC recalled that concerns regarding insufficient evidence of analytical validity and weak evidence of clinical validity and clinical utility of PD-L1 IHC testing had been raised in a previous codependent submission for later-line pembrolizumab in NSCLC (MSAC Public Summary Document (PSD) Application 1414, November 2016). MSAC considered that these concerns remained relevant to the current submission.

In considering the evidence provided to support the analytical validity of the test, MSAC noted that there is currently no PD-L1 test reference standard. MSAC recalled that, unlike many other companion tests, PD-L1 expression is measured on a continuum rather than as a dichotomous outcome (positive or negative). MSAC noted that in the current submission, a sample was considered to be positive if the TPS was ≥50%. MSAC was concerned that a per-cell threshold (i.e. weak compared to strong staining) was not defined and that the per-tumour threshold was not defined biologically.

MSAC noted that, as there is currently no reference standard for PD-L1 testing, studies reporting on the reproducibility measures of the evidentiary standard (Dako's PD-L1 IHC 22C3 pharmDx assay) were provided in the submission to address concerns regarding reproducibility of PD-L1 scoring. MSAC considered the inter- and intra-rater variability results of the Dako Reproducibility Study 1, the Dako Reproducibility Study 2, the DREAM study, and initial Australian data, and noted that Cohen's kappa coefficients for inter-observer agreement after training in the range of 0.58 to 0.68 represented modest reliability, particularly as most of the studies failed to reached their pre-defined levels of agreement. MSAC was also concerned that other than the TPS 50% threshold, a number of the criteria important for reproducibility were not defined in these studies, such as the extent of staining

in each cell contributing to the TPS count, and the biological definition of the per-tumour threshold. MSAC noted the non-constant scatter in the figures presenting the correlation of percentage tumour cell membrane staining for three commercially available assays (Ventana SP263, Dako 22C3 and Dako 28-8) reported in a 2016 study by Ratcliffe MJ et al, and considered that this raised concordance concerns. MSAC noted the comparative data for the 22C3 antibody with testing undertaken on the Ventana platform provided in the applicant's pre-ESC response and was concerned that wide variation was evident. MSAC was concerned that the concordance data presented in the submission remained insufficient to establish whether the different PD-L1 IHC assays could be used interchangeably. MSAC also considered that the potential clinical significance of misclassification from the estimated 10% discordance had not been explored.

MSAC acknowledged that the additional studies (Hirsch FR et al 2017, Scheel AH et al 2016, Adam J et al 2016, and Rimm DL et al 2017) highlighted in March 2017 correspondence from the Royal College of Pathologists of Australasia (RCPA) provided evidence to support the equivalence of the SP263, 22C3 and 28-8 clones. MSAC also noted that the applicant had advised that a number of international regulatory and reimbursement agencies have approved PD-L1 IHC testing in the context of pembrolizumab. MSAC was concerned however, that issues regarding test performance remained, and agreed with advice provided at the joint meeting of the Evaluation Sub-Committee of MSAC and the Economics Sub-Committee of PBAC (the ESCs) that the variation in reporting between laboratories may lead to samples being sent for repeat testing in different laboratories in order to gain access to pembrolizumab.

MSAC noted the March 2017 RCPA correspondence indicated that efforts to develop a Quality Assurance Program (QAP) for PD-L1 IHC in collaboration with the United Kingdom National External Quality Assessment (NEQAS) were underway. MSAC also noted concerns raised by RCPA regarding tumour heterogeneity for PD-L1 and the validity of the assay as a reliable means of patient selection.

In considering the evidence provided to support the clinical validity of the test, MSAC noted that the current submission used the clinically defined tumour response to treatment threshold from the Keynote 001 (KN-001) Phase 1 single-arm study. MSAC agreed with the concerns expressed by the ESCs that there was uncertainty regarding the applicability of the study findings to the requested population **redacted**.

MSAC noted that, in the KN-001 study, the PD-L1 expression level threshold was determined using the Receiver Operating Characteristic (ROC) curves from the Biomarker Training Set in the 'training subpopulation'. The TPS threshold of 50% for PD-L1 positivity was selected as the closest point to the optimum of all true positives and no false positives on the ROC curves (i.e. 'by maximising Youden's index'). MSAC noted that the TPS threshold was then validated with the Biomarker Validation Set in the 'validation subpopulation' of the KN-001 study. MSAC recalled that it had considered this to be a simplistic approach as it did not consider the trade-off between false positives and true positives, which should reflect the differing downstream consequences in terms of under- versus over- treatment (MSAC PSD Application 1414, November 2016). MSAC further considered that false negatives and true negatives would also result in differing downstream consequences. Overall, MSAC considered the nominated PD-L1 test to have poor performance (**redacted**% sensitivity and **redacted**% specificity for overall tumour response after 19 weeks' therapy) at the nominated threshold of 50% TPS.

MSAC recalled that the KN-001 trial showed a dose-response relationship in overall response rate to pembrolizumab with increasing PD-L1 TPS (MSAC PSD Application 1414, November 2016). MSAC was concerned that the TPS threshold may not reflect the underlying point at which biological differences become apparent. MSAC noted that patients with a lower TPS may still benefit from pembrolizumab treatment over chemotherapy even though the response may be reduced when compared to patients with a higher TPS.

MSAC noted that, following the results of the KN-001 study, the key trial in the current codependent submission, KN-024, only enrolled patients with a TPS ≥50%. MSAC noted that, in the KN-024 trial, pembrolizumab was associated with a significant benefit in patients with TPS ≥50% PD-L1 expression compared to platinum-based chemotherapy in the first-line setting. MSAC noted that the CheckMate 026 study of nivolumab in a similar setting used a lower level of PD-L1 expression (≥5%). In contrast to the KN-024 study, the CheckMate 026 trial failed to meet its primary endpoint. MSAC noted that the applicant had suggested that these contrasting results highlighted that the optimal clinical benefit of pembrolizumab is in the patient population whose tumours express high levels of PD-L1 (TPS ≥50%). MSAC considered that these findings were consistent with, but were not a validation of, the TPS 50% threshold. MSAC was concerned that the submission had not explored or replicated the lack of response in patients with a TPS <50%. MSAC agreed with the ESCs' advice that the choice of the TPS 50% threshold using the TPS scoring method remains insufficiently justified.

MSAC noted that, in contrast to EGFR and human epidermal growth factor receptor 2 (HER2), PD-L1 is part of a normal cell pathway and hence is unlikely to have a clear threshold indicating markedly different effects of associated treatments. MSAC considered that, where patients test positive for mutation biomarkers such as *EGFR*, there is a more consistent treatment effect across a range of targeted medicines. MSAC was concerned that, in contrast, variation appears evident for medicines targeting the PD-1 pathway.

MSAC also noted that pembrolizumab is currently listed in the PBS for late-stage melanoma without any requirement for companion testing to determine eligibility for treatment. MSAC noted that, in its pre-MSAC response, the applicant had indicated that the PD-L1 positive population was higher for melanoma (80%) than for NSCLC (**redacted**%) and hence relatively few patients would have been excluded if testing had been implemented for melanoma. MSAC agreed with this rationale, but remained concerned that this highlights the need for a companion test that has a good positive predictive value and negative predictive value when prevalence is lower.

In considering the evidence provided to support the clinical utility of the test, MSAC recalled its concerns regarding the stability of PD-L1 as a biomarker due to evidence of variation before and after treatment and across different stages of disease (MSAC PSD Application 1414, November 2016). MSAC noted that the submission indicated that testing for PD-L1 expression should occur at initial diagnosis with re-biopsy required for second-line treatment. However, MSAC considered that re-biopsy would not address underlying concerns regarding poor test performance.

MSAC noted that, in its pre-ESC response, the applicant provided information from a subgroup analysis of KN-024, which indicated that the benefit of pembrolizumab over platinum-based therapy was consistent across NSCLC histologies (hazard ratios for overall survival of **redacted** and **redacted**) in squamous and non-squamous, respectively). MSAC agreed that there is no data to support a role for histology in determining the clinical utility of PD-L1 expression in treatment-naïve NSCLC patients.

MSAC was concerned that the claim of codependency was not adequately supported by the data provided in the submission. MSAC noted that the KN-024 trial only included patients who had a PD-L1 positive tumour (TPS ≥50%) and hence, the treatment effect of pembrolizumab in patients with a TPS <50% could not be established. MSAC concluded that the data provided also did not allow partitioning out of the baseline prognostic performance of the test and its predictive performance in terms of pembrolizumab effect modification and, as such, neither the clinical validity nor the clinical utility of the PD-L1 as a companion test was adequately demonstrated.

MSAC concluded that it was unable to support the listing of PD-L1 IHC testing as a companion diagnostic test for selecting patients with NSCLC for treatment with pembrolizumab due to insufficient evidence of analytical validity, clinical validity and clinical utility. MSAC advised that, as PD-L1 is an imperfect biomarker, there is a likelihood that patients who might benefit from pembrolizumab treatment would be excluded by the test result.

MSAC reflected on the circumstances of this codependent application compared to other recent applications which have provided comparative clinical trial data from an "all comers" population in addition to those who test positive for a particular biomarker, which has enabled a comparison the comparative effectiveness of treatment for those who test negative for the biomarker. MSAC considered that comparative clinical trial data from such an "all comers" population would be particularly preferred for test and medicine codependencies which involve:

- expression-based biomarkers rather than mutation-based biomarkers, because of the greater uncertainty in determining a threshold of "positivity" to help determine eligibility of the medicine using expression-based biomarkers; or
- a quantitative variation rather than a qualitative variation in the treatment effect of the medicine, because predicting reduced effect is harder to detect than predicting no effect.

4. Background

MSAC considered Application 1414 - PD-L1 testing for access to pembrolizumab for the later-line treatment of locally advanced or metastatic NSCLC in November 2016. The Public Summary Document can be found on the MSAC website at www.msac.gov.au

5. Prerequisites to implementation of any funding advice

PD-L1 expression assays should be registered with the Therapeutic Goods Administration (TGA) on the Australian Register of Therapeutic Goods (ARTG).

A prerequisite to public funding is the establishment of a Quality Assurance Program (QAP) to standardise PD-L1 testing and reporting in diagnostic laboratories. The QAP would need to address interpretation of the test results for PD-L1 positivity using the other assays/antibodies likely to be available.

6. Proposal for public funding

The application provided two alternate MBS item descriptors (Table 1). The application supported a broad MBS listing (option 1), which is unchanged from the proposed item descriptor for MSAC Application 1414. The alternative MBS listing (option 2) was provided should MSAC deem the evidence for option 1 to be insufficient. Option 2 would restrict

testing to those antibodies for which MSAC considers the concordance data is adequate (e.g. 22C3 +/- 28-8 +/- SP263).

The application requested an MBS fee of $74.50 in alignment with MBS item 72848 for human epidermal growth factor receptor 2 (HER2) IHC testing; both tests require the counting of cells.

Table 1 – Proposed MBS item descriptors

Category 6 – Pathology Services
MBS item number – option 1 Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the PD-L1 antibody of tumour material from a patient diagnosed with non-small cell lung cancer to determine if the requirements relating to programmed death ligand 1 (PD-L1) status for access pembrolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $74.50 Benefit: 75% = $55.90 85% = $63.35
MBS item number – option 2 Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the 22C3 (+/- 28-8 +/- SP263) PD-L1 antibody of tumour material from a patient diagnosed with non-small cell lung cancer to determine if the requirements relating to programmed cell death ligand 1 (PD-L1) status for access to pembrolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $74.50 Benefit: 75% = $55.90 85% = $63.35

The application requested that the PD-L1 IHC test be pathologist-determinable and that an amendment be made to Note P.1.2 "Services Where Request Not Required" to include the above item number. This is consistent with other IHC tests (including ALK IHC) and with *EGFR* mutation testing of NSCLC patients, which are pathologist-determinable.

7. Summary of Public Consultation Feedback/Consumer Issues

The PICO Advisory Sub-Committee (PASC) received one response from an organisation which was supportive of the protocol.

Issues raised in the response were:

- The MBS item should be sufficiently general to include new antibodies and scoring algorithms.
- It is important that the correct scoring algorithms and cut-offs be matched with specific antibodies used in the PD-L1 test in order for consistent conclusions to be made, since this drives subsequent treatment decisions and clinical outcomes.

8. Proposed intervention's place in clinical management

The proposed clinical management algorithm included:

1) testing for PD-L1 expression at initial diagnosis;
2) use of pembrolizumab as first-line therapy for patients who are *EGFR* wildtype/*ALK* gene rearrangement negative and whose tumours express high levels of PD-L1 (TPS ≥50%).

9. Comparator

As there is currently no reference standard for PD-L1 testing, concordance between the evidentiary standard (PD-L1 IHC 22C3 pharmDx assay) and alternative PD-L1 tests was presented.

The evidence used to determine patient prognosis based on PD-L1 status and other assessments of the PD-L1 test is summarised in Table 2.

Table 2: Evidence for the test performance

Prognostic evidence	Comparison of outcomes in patients receiving usual care conditioned on the presence or absence of the biomarker	☒ k=2 SRs k=6 studies, n=2,059
Test concordance	Comparative diagnostic concordance between the PD-L1 IHC 22C3 pharmDx test and other existing PD-L1 tests	☒ k=3, n=553
Test reproducibility	Inter- and intra-rater reliability	☒ k=3, n=248
Change in patient management	Evidence to show that biomarker determination guides treatment with the drug	☐ k=0, n=0
Treatment effectiveness	Single randomised controlled trial of drug vs usual care in NSCLC patients that are PD-L1 positive	☒ k=1, n=305
Other - treatment effect modification	Phase I single-arm studies of retrospective bio-marker stratified treatment with a PD-1/PD-L1 inhibitor	☒ k=5, n=562

NSCLC = non-small cell lung cancer; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; SR = systematic review

10. Comparative safety

If PD-L1 testing was performed on tissue sections taken from a biopsy specimen obtained as part of standard diagnostic work-up, it would not incur any direct risks to patients. IHC only uses one 4-5 micron section compared to approximately 50 microns required for *EGFR* mutation testing, and so it is unlikely that a re-biopsy would be required for the PD-L1 test alone. The addition of the PD-L1 biomarker to the testing protocol at initial diagnosis would be unlikely to increase the overall re-biopsy rate.

A re-biopsy may be required due to PD-L1 expression changes following platinum-based chemotherapy or prior to retreatment with pembrolizumab. The main risk to the patient would then be complications such as pneumothorax and haemorrhage. **redacted**.

11. Comparative effectiveness

Prognostic evidence
Two meta-analyses found that patients (including Asians) with PD-L1-positive NSCLC had a worse prognosis than those with PD-L1-negative tumours.

Comparative analytical performance
To date, four different assays using four different antibodies have been used in clinical trials to determine the level of PD-L1 and/or PD-1 expression in NSCLC tumour cells and/or immune cells (Table 3). Three studies were identified that compared the accuracy of these tests.

The Dako PD-L1 IHC 22C3 pharmDx test and the Dako 28-8 pharmDx assay demonstrated high concordance with 93–95% overall agreement at both a 1% and a 50% threshold level of TPS. In contrast, the Ventana SP142 assay consistently labelled fewer tumour cells and the Ventana SP263 assay consistently labelled more cells than the other assays. Thus, the Ventana SP142 and SP263 assays would need to be carefully calibrated so that the thresholds used by the Dako assays and the two Ventana assays identify the same population for treatment with anti PD-1/PD-L1 antibodies.

Table 3: Concordance (% agreement) between the four PD-L1 IHC tests used in clinical trials

Assay	Dako 28-8		Ventana SP142		Ventana SP263	
Dako 22C3	≥1% TPS	93–95%	≥1% TPS	75–83%	≥1% TPS	70–90%
	≥50% TPS	93%	≥50% TPS	91%	≥50% TPS	85–94%
Dako 28-8			≥1% TPS	81%	≥1% TPS	91%
			≥50% TPS	91%	≥50% TPS	82%
Ventana SP142					≥1% TPS	76%
					≥50% TPS	81%

IHC = immunohistochemistry; PD-L1 = programmed death ligand 1; TPS = tumour proportion score.
Source: Scheel et al. (2016)[1], Ratcliffe et al. (2016)[2] and AACR BluePrint Study[3]

The evaluation of the application also noted that the evidence presented suggested that:

- There was little difference in the overall survival (OS) and progression-free survival (PFS) of patients who were tested using archival specimens compared to those who had a fresh specimen. The use of archival material to determine PD-L1 status may not be a cause for concern with respect to stability of the PD-L1 antigen in properly stored archival tissue blocks.
- The assays developed to determine the level of expression of PD-L1 on the surface of NSCLC tumour cells prior to treatment with pembrolizumab (Dako 22C3 assay) or nivolumab (Dako 28-8 assay) are highly concordant and could potentially be used to direct treatment with either drug.

However, the following concerns need to be addressed:

- The timing of the test. There is some evidence to suggest that PD-L1 status may differ in metastases compared to the primary tumour and may change after treatment. This suggests that testing prior to progression to Stage IIIB/IV disease may result in patients who are falsely negative missing out on potentially beneficial treatment and false positive patients receiving treatment from which they may receive little benefit.
- The clinical utility of PD-L1 testing, as requested by PASC (August 2016 meeting; MSAC application 1440 outcomes), could not be assessed due to the lack of clinical data for pembrolizumab treatment without PD-L1 testing in the first-line setting.
    - Due to the limited evidence for treatment-naïve Stage IV NSCLC patients with TPS <50% PD-L1, a prognostic effect associated with PD-L1 expression could not be ruled out, and therefore patients with TPS ≥50% in the trial treated with platinum-based chemotherapy cannot reasonably approximate an unselected population treated with platinum-based chemotherapy.
- The lack of evidence to determine the effectiveness of pembrolizumab compared with platinum-based chemotherapy in treatment-naïve patients with either squamous or non-squamous disease as requested by PASC (August 2016 meeting; MSAC application 1440 outcomes) given the differential effect shown with the nivolumab trials.
- The application requested retreatment of patients who have progressive disease after achieving an initial objective response to pembrolizumab. However, it did not request retesting of these patients to determine their current PD-L1 status. One study identified in the literature during evaluation suggests that patients who progress after

[1] Scheel AH, Dietel M, Heukamp LC, Johrens K, Kirchner T, Reu S, et al. Harmonized PD-L1 immunohistochemistry for pulmonary squamous-cell and adenocarcinomas. Mod Pathol. 2016.
[2] Ratcliffe et al. A Comparative Study of PD-L1 Diagnostic Assays and the Classification of Patients as PD-L1 Positive and PD-L1 Negative. American Association for Cancer Research (AACR) Annual Meeting 2016; April 16–20, 2016; New Orleans, LA, USA2016
[3] page 72 of the AACR BluePrint Project Summary Report (Appendix 14 of the application)

achieving an initial objective response to pembrolizumab may have reduced expression of PD-L1 and may not benefit from further pembrolizumab treatment.
- The instructions accompanying the Dako 28-8 assay test define a specimen as positive if PD-L1 expression is TPS ≥1% and does not suggest the reporting of an actual TPS. This information would not be sufficient for determining eligibility to pembrolizumab as the requested PBS restriction is for TPS ≥50% PD-L1 expression.
- In addition, different drugs in this class may have different affinities for the PD-1/PD-L1 epitope and require different PD-L1 expression thresholds for optimal clinical benefit, this information needs to be provided to the pathologist for accurate reporting and to the clinician so that the patient is treated with an appropriate PD-1/PD-L1 inhibitor.
- The concordance between the Dako assays and the Ventana SP124 test (atezolizumab) and the Ventana SP264 test (durvalumab) is weaker, with the Ventana SP124 test consistently stains less tumour cells than the other tests and the Ventana SP264 test consistently stains more. Thus, the use of the Ventana assays to determine PD-L1 expression may identify different patient populations at the required thresholds.

Claim of codependency
The application claimed that treatment guided by PD-L1 status, where PD-L1 strong positives (i.e. TPS ≥50%) are treated with pembrolizumab, and PD-L1 negatives (i.e. TPS <1%) and weakly positives (i.e. TPS 1–49%) are treated with platinum-based chemotherapy, results in improved outcomes versus the comparator, which is no testing and platinum-based chemotherapy. This was based on the application's conclusions that:
- the test is accurate,
- there is no prognostic impact of PD-L1 status (therefore patients with TPS ≥50% in the trial treated with platinum-based chemotherapy can reasonably approximate an unselected population treated with platinum-based chemotherapy),
- pembrolizumab has improved effectiveness and improved or non-inferior safety, when compared to platinum-based chemotherapy and
- that there is treatment effect variation by PD-L1 status.

MSAC and PBAC have raised important concerns regarding a previous pembrolizumab codependent application for later-line NSCLC (MSAC Public Summary Document (PSD) Application 1414, November 2016 and Item 6.05 November 2016 PBAC Meeting). These concerns have relevance to the current pembrolizumab codependent application for first-line NSCLC.

12. Economic evaluation

A modelled economic evaluation, in terms of incremental cost per life year gained and incremental cost per quality-adjusted life year (QALY) gained, was presented based on the claim of superior effectiveness and safety compared to platinum-doublet chemotherapy in treatment-naïve NSCLC patients who expressed high levels of PD-L1 (TPS ≥50%). The application presented an ICER of $**redacted**/QALY based on OS and PFS outcome data from the KN-024 trial, extrapolated to 7 years duration (from median 11 months in the trial) and utility weights from the KN-024 trial.

13. Financial/budgetary impacts

An epidemiological approach was used in the submission to estimate the number of patients eligible for PD-L1 testing and pembrolizumab treatment each year, over a five-year period. The estimated number of patients eligible for PD-L1 testing is shown in Table 4.

Table 4: Estimated number of patients tested for PD-L1 expression

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of incident NSCLC cases (all stages)	10,831	11,167	11,512	11,860	12,211
Prevalent Stage IIIB/IV patients tested from prior year	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Total patients tested	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**

Note: due to insufficient data provided regarding how prevalent cases were estimated, the number of prevalent Stage IIIB/IV patients tested from the year prior could not be revised.

The evaluation noted that the expected number of patients tested presented in Table 4 may be an underestimate; patients who progressed to Stage IIIB/IV from an earlier stage were not included in the projections (only incident cases of Stage IIIB/IV in all years, and half of prevalent Stage IIIB/IV cases in year 1). If testing is intended to be performed at initial diagnosis, all NSCLC patients (regardless of stage) should be included in the expected number of tests unless the item descriptor limits testing to patients diagnosed with Stage IIIB/IV disease.

The proposed MBS fee for PD-L1 testing is $74.50, based on the fee for an item that uses similar resource requirements (scoring and reporting), MBS 72848.

The pre-MSAC response provided updated financial estimates for the net cost to the MBS (Table 5).

Table 5: Estimated cost of PD-L1 testing to the MBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Cost of PD-L1 testing	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Cost of additional biopsy/AE	**$redacted**	-	-	-	-
Net cost to the MBS	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**

14. Key issues from ESC for MSAC

The joint meeting of the ESCs noted the application to list PD-L1 immunohistochemistry (IHC) testing in the MBS was part of an integrated codependent application, which also requested that the PBAC consider the listing of pembrolizumab in first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC).

The ESCs noted that MSAC had raised concerns regarding insufficient evidence of analytical validity and weak evidence of clinical validity and clinical utility for PD-L1 IHC testing in a previous codependent application for later-line pembrolizumab in NSCLC (MSAC Public Summary Document (PSD) Application 1414, November 2016). The ESCs considered that these concerns remain relevant to the current application and are well described in the evaluation of the application and in the PSD from the November 2016 MSAC meeting.

The ESCs agreed with the evaluation of the application that the argument presented to support treatment effect modification by PD-L1 status in treatment-naïve patients was not well supported.

The ESCs considered that concerns regarding the reproducibility and reliability of PD-L1 IHC remained the key issue for MSAC. The ESCs noted that variation in reporting between laboratories may also occur as a result and expressed concern that this may lead to samples

being sent for repeat testing in different laboratories in order to gain access to pembrolizumab.

The ESCs noted that the application included both a generic and specific PD-L1 antibody assay option for the proposed MBS item descriptor. The ESCs re-considered their concerns regarding the interchangeability of the available tests (as noted in the Blueprint study) and maintained that this issue may lead to further implementation issues as new PD-1 inhibitor medicines become available. Concordance data remained insufficient to establish whether the different PD-L1 IHC assays could be used interchangeably.

The ESCs also noted that this will lead to the requirement for a Quality Assurance Program to address interpretation of the test results for PD-L1 positivity using all assays/antibodies likely to be available. The ESCs noted that the Royal College of Pathologists of Australasia (RCPA) did not endorse the use of PD-L1 testing as a biomarker (MSAC PSD for Application 1414), making it difficult to establish an inter-laboratory quality assurance program to manage the performance issues identified.

The NSCLC cohort of the Keynote 001 (KN-001) trial was used to define and validate a PD-L1 expression level associated with clinical benefit from pembrolizumab. The ESCs noted that QUADAS-2 assessment had not been undertaken for this trial, such that there was a potential for high risk of bias and for applicability. MSAC noted that a QUADAS-2 assessment was provided with the pre-MSAC response.

The ESCs noted that four PD-L1 expression scoring methods were explored with receiver operator characteristics (ROC) curve analysis in KN-001 with the tumour proportion score (TPS) method selected.

The reference standard used in the ROC analysis was response to pembrolizumab based on investigator-assessed overall response rate (ORR) measured at 19 weeks. The ESCs considered that this is a surrogate outcome measured at an interim timepoint and questioned whether ORR in KN-001 was predictive of progression-free survival or overall survival.

The ESCs noted that the NSCLC cohort of the KN-001 had a small sample size, limited information on the flow of patients and no information on patients excluded from analysis.

The intended purpose of PD-L1 IHC testing in KN-001 was to evaluate the efficacy of pembrolizumab in patients whose tumours expressed a high level of PD-L1. The ESCs considered that this may raise applicability issues as the proposed place in clinical management is to determine the eligibility of patients to pembrolizumab therapy.

The PD-L1 expression level thresholds were determined using a Biomarker Training Set in the 'training subpopulation' and then validated with the Biomarker Validation Set in the 'validation subpopulation'. The ESCs noted that variations in PD-L1 expression levels and treatment experience were evident between these populations. The ESCs considered that this variability raises concerns regarding the generalisability of the training subpopulation to the requested MBS/PBS population. The ESCs advised that further information on the clinical characteristics of the training subpopulation may assist in addressing these concerns.

The ESCs questioned why the area under the curve for the ROCs was not reported for each expression scoring method and noted that the ROC for the TPS diverges from the other three methods at low values. The ESCs also questioned the proposed TPS threshold of 50% based on maximisation of Youden's J statistic as other scoring methods are associated with lower

thresholds using this approach. The ESCs noted that it was unlikely that data on false negative rate or false positive rate by thresholds would be possible for this biomarker.

The ESCs noted that the TGA had approved both the Dako PD-L1 IHC 22C3 pharmDx assay and the Dako PD-L1 IHC 28-8 pharmDx assays on 17 November 2016. The ESCs noted that a TPS threshold was not stipulated as part of the TGA approval.

The ESCs considered that the appropriate TPS threshold for access to pembrolizumab was more a matter for PBAC than for MSAC. However, the ESCs noted that the choice of the threshold using the TPS method of 50% remains insufficiently justified.

The ESCs noted that the proposed MBS fee ($74.50) may be overestimated given that the fee for IHC test items is driven by the number of antibodies used per specimen.

The ESCs considered the financial impact on the MBS to be underestimated as patients who progressed to Stage IIIB/IV NSCLC from an earlier stage were not included in the projections. The ESCs noted that a proportion of prevalent cases had been included in Year 1 only and advised that projections for this population out to Year 5 should be included. The ESCs also noted that no costs for re-testing or re-biopsy were included.

The ESCs noted that questions around whether or not this service should be pathologist determinable, remained important policy issues.

The ESCs suggested that it would be valuable if the sponsor could provide more information on the KN-001 study, specifically:

- the AUC (with 95% CI) for each ROC
- a table of true positive rate and false positive rate by TPS thresholds, for the full range of threshold values (including ≥1%)
- the clinical characteristics of the 'training subpopulation', including information on cancer staging
- comment on the interpretation of the biomarker validation given that it was based on a surrogate outcome measured at an interim time point.

The item specific consumer comments presented requested a comprehensive approach be taken to informing consumers around testing, treatment and costings to allow informed consent.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

MSD is disappointed with the outcome, particularly given the test is registered and available for use in Australia as well as being included in overseas guidelines to determine eligibility for treatment with PD-1 therapies (pembrolizumab and nivolumab) for lung cancer. It is particularly concerning that the unique requirements for co-dependent technologies being imposed through the Australian reimbursement system are delaying access to a medicine that has been deemed by MOGA to have the highest possible rating of clinical benefit (5 out of 5) using the ESMO Magnitude of Clinical Benefit Scale. MSD will endeavour to work through the issues with MSAC so that NSCLC patients whose tumours are strongly PD-L1 positive can get access to pembrolizumab as soon as possible.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website