



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1440.1- PD-L1 testing for access to pembrolizumab in treatment naïve patients with locally advanced or metastatic non-small cell lung cancer

Applicant: Merck, Sharp & Dohme (Australia) Pty Ltd

Date of MSAC consideration: MSAC 71st Meeting, 23 November 2017

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

The integrated codependent resubmission requested:

- Medicare Benefits Schedule (MBS) listing of immunohistochemistry (IHC) testing for the evaluation of programmed cell death ligand 1 (PD-L1) expression in patients diagnosed with metastatic non-small cell lung cancer (NSCLC); and
- Section 100 (Efficient Funding of Chemotherapy [EFC]) Authority Required Pharmaceutical Benefits Scheme (PBS) listing for first-line treatment with pembrolizumab of those patients with a performance status of 0 or 1, 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 whose IHC results show evidence of high levels of PD-L1 expression, defined as a tumour proportion score (TPS) of $\geq 50\%$.

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 deferred its advice until such time as PBAC subsequently decides to recommend the PBS listing of pembrolizumab for this population. MSAC foreshadowed its support for a new MBS item for the immunohistochemistry testing of programmed cell death ligand 1 (PD-L1) expression to help determine eligibility for PBS-subsidised pembrolizumab in patients with locally advanced or metastatic NSCLC.

MSAC advised that an MBS fee of \$74.50 would be appropriate as the test requires quantitative assessment.

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

MSAC noted that this was a resubmission for an application which it did not support in April 2017 to list programmed cell death ligand 1 (PD-L1) immunohistochemistry (IHC) testing in

the MBS ([MSAC PSD Application 1440, April 2017](#)). MSAC recalled it had not previously supported the application because it considered PD-L1 testing to be a poor companion diagnostic test with insufficient evidence of analytical and clinical validity, and clinical utility. MSAC also recalled that it considered PD-L1 to be such an imperfect biomarker it might exclude patients who may benefit from pembrolizumab from treatment.

MSAC considered that the development of a Royal College of Pathologists (RCPA) quality assurance program which is currently in the pilot stage had addressed one of its concerns. However, the most influential development since the previous consideration was the PBS listing of an alternative PD-L1 inhibitor, nivolumab, for second-line treatment of patients with metastatic NSCLC whose disease had progressed following treatment with platinum-based chemotherapy without there being a requirement for PD-L1 testing. This changed the clinical utility consequences of poor PD-L1 IHC test performance, because most patients with advanced NSCLC who test negative (correctly or not) for treatment with pembrolizumab would now have access to nivolumab in due course.

As a result, MSAC considered that supporting PD-L1 testing for access to pembrolizumab was unlikely to cause harm provided the risk and benefit profiles of pembrolizumab and nivolumab are similar. MSAC noted that decisions about the comparative safety and effectiveness of the two medicines fell within the remit of the PBAC.

MSAC accepted that PD-L1 testing would pose no direct safety risks to patients because it would be carried out using tissue samples taken as part of standard diagnostic work-up for patients first presenting with metastatic NSCLC. However, MSAC noted that there may be some risk of pneumothorax or haemorrhage should a patient need to be re-biopsied to determine eligibility for pembrolizumab treatment. MSAC noted that this may sometimes be necessary in patients diagnosed with earlier stage NSCLC who subsequently develop metastases. However, the availability of nivolumab (which doesn't require PD-L1 immunostaining results) will allow the treating clinician to balance the risks of pursuing a PDL-1 result to potentially confirm eligibility for first line pembrolizumab vs considering immunotherapy in unselected patients as second line therapy. MSAC noted the economic model was driven by the cost of pembrolizumab rather than PD-L1 IHC testing. Sensitivity analyses which varied the prevalence of PD-L1 positivity within the patient population, or varied the sensitivity and specificity of PD-L1 testing, also had little impact upon cost-effectiveness. In addition, MSAC noted the costs of re-biopsy or re-testing would have little impact upon cost-effectiveness.

Paragraph redacted

MSAC noted that the net cost to the MBS for PD-L1 IHC testing would be highest in year 1 due to the large number of prevalent patients requiring testing: **redacted** patients at an MBS cost of ~\$**redacted**. MSAC noted that MBS costs would fall to approximately \$**redacted** per year in the following four years.

MSAC advised that the appropriate fee for the test should be \$74.50, in line with MBS item 72848 (IHC of one, two or three of the oestrogen, progesterone or *HER2* antibodies). MSAC considered the higher fee was justified because the test requires counting of cells and assessment of staining intensity.

Consistent with the proposed PBS restriction for pembrolizumab, MSAC advised that the MBS item descriptor stipulate that patients being tested for PD-L1 should have metastatic NSCLC with a WHO performance status of 0 or 1, and should already have tested negative for both *EGFR* gene mutations and *ALK* gene rearrangements. MSAC also recommended a more generic item descriptor which covered the use of any suitable PD-L1 antibody. Specifically:

Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the programmed cell death ligand 1 (PD-L1) antibody of tumour material from a patient diagnosed with metastatic non-small cell lung cancer, with a WHO performance status of 0 or 1, and who does not have either an activating epidermal growth factor (EGFR) mutation or an anaplastic lymphoma kinase (ALK) gene rearrangement, to determine if the requirements relating to PD-L1 status for access to pembrolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

For clarity for those interpreting the results of the PD-L1 IHC test, MSAC also suggested that an administrative note accompanying the MBS item descriptor provide the threshold TPS beyond which the tested patient could be considered eligible for pembrolizumab.

4. Background

At its March 2017 meeting, MSAC considered Application 1440 - PD-L1 testing for access to pembrolizumab for treatment naïve locally advanced or metastatic NSCLC.

MSAC did not support public funding of PD-L1 IHC as a companion diagnostic test for selecting patients with 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.

At its November 2016 meeting, MSAC considered Application 1414 - PD-L1 testing for access to pembrolizumab for the later-line treatment of locally advanced or metastatic NSCLC.

The Public Summary Documents (PSDs) for these applications 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).

Registration of the PD-L1 22C3 pharmDXTM kit was approved by the TGA on 17 November 2016. This kit is intended for use in the detection of PD-L1 protein in formalin-fixed paraffin-embedded (FFPE) NSCLC tissue using the Dako Autostainer Link 48 platform as an aid in identifying NSCLC patients for treatment with pembrolizumab.

The SP263, SP142 and 28-8 antibody kits are also registered by the TGA. The SP263 antibody is TGA approved to determine eligibility for pembrolizumab and nivolumab.

A prerequisite to public funding is the establishment of a Quality Assurance Program (QAP) to standardise PD-L1 testing and reporting in diagnostic laboratories. A pre-pilot QAP has been conducted with 14 pathologists, but the results are not yet available.

6. Proposal for public funding

To address MSAC concerns, the resubmission proposed two MBS item options (see Table 1) as per the previous submission:

- A broad item number including all PD-L1 antibodies (preferred by the resubmission). This is in-line with MSAC preferences for the listing of tests and is consistent with the PICO confirmation.

- A narrow item number limiting reimbursement to PD-L1 antibodies that MSAC considers are sufficiently concordant.

Table 1: Proposed MBS item

Category 6 – Pathology Services
<p>MBS item number</p> <p>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 cell death ligand 1 (PD-L1) status for access to pembrolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>Fee: \$74.50 Benefit: 75% = \$55.90 85% = \$63.35</p>
<p>MBS item number</p> <p>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.</p> <p>Fee: \$74.50 Benefit: 75% = \$55.90 85% = \$63.35</p>

The resubmission requested an MBS fee of \$74.50 in alignment with MBS item 72848 for human erbB-2 (HER2) IHC testing because both tests require the counting of cells.

The resubmission requested that the PD-L1 IHC test be a pathologist determinable test 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 and *EGFR* mutation testing of NSCLC patients, which are pathologist determinable.

The critique noted that, given the concerns about the stability of PD-L1 expression levels, the committee may wish to consider whether testing should occur after patients are diagnosed with or progress to metastatic NSCLC and their tumours are *EGFR* negative and *ALK* negative (i.e. when the determination of their PD-L1 status is required to decide whether they are eligible for treatment with pembrolizumab).

7. Summary of public consultation feedback/consumer issues

See Application 1440 PSD on the MSAC website at www.msac.gov.au.

8. Proposed intervention’s place in clinical management

Lung cancer is the fifth most commonly diagnosed invasive cancer and is the leading cause of cancer death in Australia. It is estimated that 12,434 new cases of lung cancer will be diagnosed in 2017 in Australia and that the estimated number of deaths will be 9,012. The target population for PD-L1 testing is patients diagnosed with NSCLC. This remains the same as in the previous submission.

The median prevalence of PD-L1 TPS $\geq 50\%$ for both Australia and the broader Caucasian population prevalence is 26% (range 22–29) and 29% (range 25–30), respectively. These values are consistent with the proposed prevalence of 28.5% for the base case in the economic evaluation.

In the clinical management algorithm, all patients suspected of having NSCLC will undergo a biopsy at initial diagnosis to determine histology. For patients with NSCLC of squamous histology, assessment of PD-L1 status through IHC will be the only biomarker test

undertaken at diagnosis. For patients who have non-squamous or not otherwise specified NSCLC, PD-L1 IHC testing will be performed at initial diagnosis, along with *EGFR* and *ALK* testing.

9. Comparator

The re-submission nominated current practice, i.e. no test and treatment with platinum-based doublet chemotherapy for all patients, as the main comparator. This is unchanged from the previous submission.

10. Comparative safety

As PD-L1 testing is to be 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 in patients diagnosed at an earlier stage disease and receiving subsequent treatment. The main risk to the patient would then be complications such as pneumothorax and haemorrhage. However, the critique noted that if cytology samples (fine needle aspirations and effusions) were used for PD-L1 testing, the associated risks would be reduced.

11. Comparative effectiveness

The resubmission presented a linked evidence approach to show that targeting of PD-L1 with the medicine will improve health outcomes, see Table 2.

Table 2: Evidence provided in the submission to support the use of the codependent technology

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical trials
Accuracy and performance of the test (analytical validity)	A study of test accuracy with the evidentiary standard using the 50% TPS threshold	☒ k=5 n=700	k=3 low risk of bias k=2 unclear risk of bias
Prognostic evidence	Comparison of outcomes in patients receiving usual care conditioned on the presence or absence of the biomarker	☒ k=8 n=12,939	Low risk of bias
Change in patient management	Evidence to show that biomarker determination guides decisions about treatment with the medicine	☒ k=1 n=545	PFS: low risk of bias OS: risk of confounding (significant treatment switching) Safety, QoL: High risk of bias
Treatment effectiveness			
Predictive effect	Comparison of outcomes in patients with or without the biomarker who receive the medicine or its comparator	☒ k=2 n=142	High risk of bias, unadjusted indirect comparison
Treatment effect (enriched)	Single randomised controlled trial of medicine vs usual care in patients that are test positive in both arms	☒ k=1 n=545	PFS: low risk of bias OS: risk of confounding (significant treatment switching) Safety, QoL: High risk of bias
Other	Single arm PD-L1 unselected chemotherapy trials versus KN-001 and KN-024	☒ k=8 n=2,129	High risk of bias; unadjusted indirect comparison

a reference standard available; b reference standard not available; k=number of studies, n=number of patients.

No evidence was presented on the effectiveness of the comparator in a biomarker negative population, see Table 3. The evidence provided for the effectiveness of pembrolizumab in a biomarker negative population is also limited to a few treatment naïve patients enrolled in a phase II trial (KN-001). The resubmission provided new evidence on the effectiveness of the comparator in a biomarker unselected population as a surrogate for the biomarker negative population.

The critique noted that biomarker positive is defined as TPS $\geq 50\%$ which comprises approximately 26% -29% of the population in Australia; meaning that an unselected population would consist primarily of patients without PD-L1 expression (~50%) and also patients with PD-L1 expression, but below the TPS 50% threshold (~25%).

Table 3: Data availability to inform comparisons

Proposed test vs no test	No studies	
Proposed test vs alternative test	Ratcliffe et al, 2017; Rimm et al, 2017; Adam et al, 2016; Scheel et al, 2016	
	Pembrolizumab	Platinum doublet chemotherapy
Biomarker test positive	KN-024, KN-001	KN-024
Biomarker test negative	KN-001	No studies
Biomarker unselected	No studies	Gronberg, 2009; Sandler, 2000; Scagliotti, 2008; Thomas, 2006; Yamamoto, 2006; Zatlouka, 2003

The critique noted that the studies by Rimm et al. (2017) and Adam et al. (2016) provide new concordance data, comparing the four commercially available tests and comparing laboratory developed tests (LDTs) with the evidentiary standard and partially addresses previous MSAC concerns about test concordance.

The critique stated that the studies enrolling biomarker-unselected patients receiving platinum-doublet chemotherapy also provide new evidence, but are a poor surrogate for biomarker negative studies and the baseline characteristics of the patients enrolled in these studies are highly variable. Therefore, the unadjusted indirect comparisons, undertaken with these studies, are subject to a high risk of bias and do not provide any conclusive evidence.

The critique noted that the risk of bias and confounding in KN-024 differed for the different treatment outcomes:

- There was a low risk of bias for PFS, as disease progression was determined by independent radiologists without knowledge of patient treatment assignment.
- Assessment of OS had a low risk of confounding. Although patients randomised to the chemotherapy arm were allowed to receive second-line pembrolizumab upon progression, the treatment switching would reflect current clinical practice.

Assessment of subjective safety outcomes and other patient-reported quality of life (QoL) outcomes were likely to be biased given that patients and investigators were aware of treatment allocation.

Prognostic evidence

Three meta-analyses found that Asian patients with PD-L1-positive NSCLC had a worse prognosis than those with PD-L1-negative tumours.

A meta-analysis of five studies found a trend favouring overall survival in Caucasian patients with tumours expressing PD-L1 compared with those whose tumours do not express detectable levels of PD-L1.

Comparative analytical performance

The critique noted that the concerns about the analytical validity of the Dako 22C3 assay against a reference standard (MSAC 1440 PSD) were not addressed further in the resubmission. This is due to the lack of an appropriate reference standard.

MSAC determined that the PD-L1 assay had poor performance at a 50% threshold with 75% sensitivity and 75% specificity based on a comparison with a clinical reference standard of overall tumour response after 19 weeks' therapy (MSAC Application1440 PSD, page 3). While this represents the predictive accuracy of the test plus the treatment, it does not reflect the diagnostic accuracy of the test on its own.

The evidentiary standard was the Dako 22C3 assay used to determine eligibility for enrolment in the KN-024 trial, which provided the main clinical effectiveness evidence.

Table 4: Comparative analytical validity of available PD-L1 tests compared with the evidentiary standard

Accuracy of commercially available PD-L1 tests using the same nominated TPS threshold for both tests			
Evidentiary standard: Dako 22C3 assay			
	Dako 28-8	Ventana SP263	Ventana SP142
Estimated sensitivity			
Scheel et al. 92016)	1%: 98% (95%CI 93, 100) 50%: 81% (95%CI 64, 92)	1%: 100% (95%CI 96, 100) 50%: 100% (95%CI 90, 100)	1%: 79% (95%CI 70, 87) 50%: 75% (95%CI 58, 88)
Estimated specificity			
Scheel et al. 92016)	1%: 86% (95%CI 70, 95) 50%: 97% (95%CI 91, 99)	1%: 63% (95%CI 45, 79) 50%: 80% (95%CI 71, 87)	1%: 94% (95%CI 81, 99) 50%: 97% (95%CI 91, 99)
	Dako 28-8	Ventana SP263	Ventana SP142
Prevalence rates ^a	22%, 28,5%, 30%	22%, 28,5%, 30%	22%, 28,5%, 30%
Estimated positive predictive value at the above prevalence rates (TPS ≥50%)			
Scheel et al. (2016)	88%, 92%, 92%	59%, 67%, 68%	88%, 91%, 91%
Estimated negative predictive value at the above prevalence rates (TPS ≥50%)			
Scheel et al. (2016) ^b	95%, 93%, 92%	100%	93%, 91%, 90%

^a Prevalence rates used was the prevalence of TPS ≥50% in the Australian cohort from the KN-o24 trial (28.5%), and the lowest and highest estimated prevalence rates from studies included to determine median prevalence in Australian and Caucasian studies.

The critique noted that, as the true sensitivity and specificity of the evidentiary standard has yet to be determined, the proportion of false negative and false positive results obtained by the individual tests cannot be conclusively determined.

Table 5: Comparative analytical concordance of various PD-L1 tests compared with the evidentiary standard

	22C3	28-8	SP263	SP142	E1L3N
Weighted kappa 1% and 50% TPS threshold					
Adam et al. (2017)	Ref: Dako 22C3 Dako: 0.82–0.91 LDT-Ventana: 0.77–0.81 LDT-Leica: 0.50– 0.62 Overall: 0.73	Ref: Dako 28-8 Dako: 0.79–0.94 LDT-Ventana: 0.73–0.80 LDT-Leica: 0.58– 0.60 Overall: 0.73	Ref: Ventana SP263 Ventana: 0.81 LDT-Dako: 0.83– 0.86 LDT-Leica: 0.83– 0.86 Overall: 0.81	Ref: Ventana SP263 LDT-Dako: 0.38– 0.68 LDT-Ventana: 0.43–0.45 LDT-Leica: 0.78– 0.81 Overall: 0.64	Ref: Ventana SP263 LDT-Dako: 0.63– 0.77 LDT-Ventana: 0.60–0.81 LDT-Leica: 0.75– 0.78 Overall: 0.78
Overall percent agreement for combined, 1% or 50% TPS threshold					
Ratcliffe et al. (2017)		1%: 94% (lower 95%CI 92) 50%: 97% (lower 95%CI 96)	1%: 91% (lower 95%CI 89) 50%: 94% (lower 95%CI 91)		
Scheel et al. (2016)		Combined: 72% 1%: 95% 50%: 93%	Combined: 56% 1%: 90% 50%: 85%	Combined: 56% 1%: 83% 50%: 91%	
Positive percent agreement					
Ratcliffe et al. (2016)			50%: 84% (lower 95%CI 77)		
Scheel et al. (2016)		1%: 93% 50%: 93%	1%: 88% 50%: 64%	1%: 74% 50%: 69%	
Negative percent agreement					
Ratcliffe et al. (2016)			50%: 97% (lower 95%CI 95)		
Scheel et al. (2016)		1%: 81% 50%: 91%	1%: 88% 50%: 64%	1%: 74% 50%: 69%	

The concordance between the Dako 22C3, Dako 28-8 and Ventana SP263 at a 50% TPS threshold was high with the overall percent agreement (OPA) being 94–97% for all comparisons in the study by Ratcliffe et al. (2017) and 85–93% in the study by Scheel et al. (2016). The OPA between Ventana SP142 and other three assays was slightly lower and ranged from 81% to 91% in the study by Scheel et al. (2016).

In the study by Adam et al. (2017), the concordance between centres using the commercial tests and LDTs using the same antibodies for 22C3, 28-8 and SP263 was good to very good (weighted kappa 0.73–0.81). The overall concordance between the Ventana SP263 assay and LDTs for E1L3N and SP142 antibodies was also good (weighted kappa 0.78 and 0.64, respectively). However, there was greater variability between centres with most results on the Dako and Ventana platforms being less concordant than using the Leica platform, indicating the need for caution if using the E1L3N and SP142 antibodies for PD-L1 testing.

Overall, the critique considered that the evidence provided for concordance for PD-L1 testing using both commercial assays and LDTs, especially if using the antibodies 22C3, 28-8 or SP263, together with the use of a QAP provides stronger support for PD-L1 testing results being equivalent between diagnostic laboratories than in the previous submission.

Clinical claim

In Stage IV NSCLC patients whose tumours express PD-L1 ($\geq 50\%$) and are EGFR wild-type and ALK translocation negative, pembrolizumab is more effective than platinum doublet at improving progression-free survival, overall survival and safety.

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 Stage IV NSCLC patients who expressed high levels of PD-L1 (TPS $\geq 50\%$).

The resubmission presented an incremental cost-effectiveness ratio of \$**redacted** /QALY based on OS and PFS data from the KN-024 trial, extrapolated to 7.5 years duration (from median 19 months in the trial) and utility weights from the KN-024 trial. The base case economic model did not consider cost for re-biopsy or re-testing.

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the number of patients eligible for PD-L1 testing and pembrolizumab treatment each year, over a six-year period. The resubmission assumed that the number of patients eligible for testing was based on the number of incident NSCLC cases. In the first year of listing, catch up testing was assumed in prevalent patients with earlier stages of disease in the year prior to listing who subsequently experience disease progression to Stage IV disease.

The estimated number of patients eligible for PD-L1 testing is shown in Table 6.

Table 6: Estimated number of patients treated for PD-L1 expression

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of incident NSCLC cases (all stages)	redacted	redacted	redacted	redacted	redacted	redacted
Prevalent Stage IIIB/IV patients tested from prior year	redacted	redacted	redacted	redacted	redacted	redacted
Total patients tested	redacted	redacted	redacted	redacted	redacted	redacted

NSCLC = non-small cell lung cancer

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.

Costs associated with re-biopsy and treatment of biopsy-related adverse events (AEs) in prevalent patients as well as costs for chemotherapy administration and disease management were also included in estimating the net cost to the MBS.

Table 7: Estimated net cost to the MBS and to the Government^a

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cost of PD-L1 testing	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost of re-biopsy and management of biopsy-associated AE	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net cost to the MBS Revised^b	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net cost to the PBS/RPBS Revised ^c	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net cost to the Government Revised^{b,c}	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

AE = adverse event

^a Including patients co-payments

^b Estimates were revised during the evaluation by including costs for disease management and drug administration

^c Estimates were revised during the evaluation by amending the number of patients who would switch from first-line doublet chemotherapy to second-line nivolumab

It was estimated that, if PD-L1 testing and pembrolizumab were both listed; the net cost to the MBS would be approximately \$redacted in the first year of listing, decreasing to \$redacted in Years 2-6.

From Year 2 to Year 6, it was estimated that nil prevalent patients from the prior year who progress to Stage IV NSCLC in the subsequent year would require re-biopsy and/or PD-L1 testing, as the resubmission assumed that all the prevalent patients would have had their PD-L1 status determined at initial diagnosis, using tissue from the diagnostic biopsy.

The critique considered that this may result in an underestimate of the net cost to the MBS in Years 2-6 of listing. The resubmission's approach did not capture testing of patients diagnosed with an earlier stage of NSCLC prior to Year 1 of listing who subsequently progress to Stage IV disease in Year 2 to Year 6.

14. Key issues from ESC for MSAC

The ESCs noted that this was a resubmission for an application that MSAC did not support in April 2017 due to insufficient evidence of analytical and clinical validity, and clinical utility.

The ESCs noted that the MBS item descriptor should limit the use of PD-L1 testing to patients with negative *EGFR* and *ALK* results.

The ESCs noted that many of the issues identified in the previous submission had been addressed, but that some concerns remained.

The ESCs noted that the lack of a reference standard for PD-L1 testing had not been addressed further in the resubmission. Due to the lack of a reference standard, the evidentiary standard used in the resubmission is the same as used previously, i.e. the Dako PD-L1 IHC 22C3 pharmDx assay (Dako 22C3). The ESCs noted that there are currently no other biomarker tests that can be used to predict response to pembrolizumab in NSCLC.

The ESCs noted that it was still unclear whether there was any prognostic effect associated with PD-L1 status. The critique had undertaken a meta-analysis of seven studies carried out in Caucasian populations which used a variety of TPS thresholds, and the ESCs noted that while there was a trend towards increased survival among patients with tumours expressing PD-L1, this failed to reach statistical significance.

The ESCs noted that, because no PD-L1 negative (defined as TPS <50%) patients were enrolled into the Keynote-024 (KN-024) study comparing pembrolizumab with chemotherapy among patients with previously untreated stage IV NSCLC, information about patients who were falsely classified as TPS <50% (false negatives) was lacking.

The ESCs noted that the choice of the 50% TPS threshold remained insufficiently justified and that it was still not possible to establish whether people with a TPS <50% may benefit from pembrolizumab treatment. The applicant presented indirect naïve comparisons of treatment response and survival among PD-L1 unselected patients undergoing chemotherapy, patients with TPS <50% treated with pembrolizumab from the Keynote-001 (KN-001) study and patients with TPS ≥50% treated with pembrolizumab from the KN-024 study. The ESCs noted that baseline characteristics of patients included in each group differed markedly across the studies and these had not been adjusted for in the analyses. The ESCs noted that this lack of clear evidence around benefit in people with TPS <50% means there could be leakage if people with a TPS <50% are treated with pembrolizumab.

The ESCs noted that there was clinician support for the 50% TPS threshold, and that a revised statement from the Royal College of Pathologists (RCPA) had indicated that, while the RCPA remained concerned that patients with NSCLC who may benefit from treatment could be excluded from treatment on the basis of an imperfect biomarker, it accepted that PD-L1 is the best biomarker currently available.

The ESCs noted that MSAC had been concerned that there was insufficient evidence to establish concordance between the different antibodies and assays/platforms in the previous submission. The ESCs noted that the resubmission provided information on observer overall percent agreement (OPA) at a TPS threshold of 50% in two studies comparing the different commercially available assays (Dako 22C3, Dako 28-8 and Ventana SP263). Concordance was high with OPAs of 94–97% reported in Ratcliffe MJ et al 2017 and 85–93% reported in Scheel AH et al 2016. The ESCs noted that concordance between the commercial assays and laboratory developed tests (LDTs) for the 22C3, 28-8 and SP263 antibodies was good with weighted kappas of 0.73–0.81 reported (Adams J et al 2016). However, that there was greater variability with the SP142 and E1L3N antibodies with weight kappas ranging from 0.38–0.81 reported on Dako, Ventana and Leica platforms (Adams J et al 2016).

The ESCs noted that MSAC had raised concerns about reproducibility of test results between different laboratories and pathologists. The ESCs noted that the resubmission clarified that using the 50% TPS threshold, the two Dako reproducibility studies and the DREAM study

(Cooper WA et al 2017) all achieved overall inter-observer agreement levels of 80% or more while three studies reported good inter-observer kappa values of 0.6–0.8 (Cooper WA et al 2017; Scheel AH et al 2016; Cooper WA et al 2015).

The ESCs noted that studies investigating the heterogeneity of PD-L1 expression within a specimen block indicated concordance for PD-L1 expression varied from moderate to high (Dako Appendix 29 study; Rehman JA et al 2017; Casadevall D et al 2017).

The ESCs noted that concerns surrounding the reproducibility of PD-L1 testing between fresh and archival tissue PD-L1 testing had been reasonably addressed. One study reported no difference in overall survival among patients enrolled in the Keynote-010 (KN-010) study on the basis of fresh or archival tissue (Herbst RS et al 2016), while another study found similar levels of PD-L1 expression between fresh and archival samples up to three years old (Midha A et al 2016).

The ESCs noted that emerging evidence suggested that cytology samples may be suitable for PD-L1 testing. In three studies in which cytology samples were compared with biopsy or surgical resection samples from the same lesion, concordance at the 1% or 50% TPS thresholds was 85% or higher (Skov BG & Skov T 2017; Heymann JJ et al 2017; Ile M et al 2017). The ESCs noted that use of cytology for testing may reduce adverse events and costs. The ESCs noted that this would be the first time that cytology testing for access to a PBS medicine would be funded in the MBS should MSAC support this use.

The ESCs noted that, in seven studies which looked at heterogeneity between paired primary tumour and metastatic samples, the OPA concordance rates ranged from 63% to 100% and that this level of heterogeneity was similar to that seen for other biomarkers (*EGFR* and *KRAS* mutations) that are currently MBS subsidised.

The ESCs noted that there was evidence that PD-L1 status can vary with disease progression and after treatment with radiotherapy, chemotherapy and treatment with tyrosine kinase inhibitors (TKIs). The ESCs considered that this has implications for decisions as to when to investigate PD-L1 status — i.e. whether testing should be delayed until patients have progressed to stage IV disease or whether patients should be re-biopsied once they progress to stage IV disease.

The ESCs noted that the RCPA is in the process of setting up a Quality Assurance Program (QAP) for PD-L1 testing, and that a ‘pre-pilot’ study involving 14 participants had been completed but the results had not been released. The ESCs considered that the release of these results would assist in determining the quality and reproducibility of PD-L1 testing currently available in Australia.

The ESCs noted that MSAC had been concerned that variation between laboratories may lead to repeat testing of samples in different laboratories in order to gain access to pembrolizumab. The ESCs noted that the applicant had obtained advice from pathologists that this does not happen with current biomarker tests and would be unlikely to occur for PD-L1 testing. The ESCs considered that, once testing was standardised under a QAP, this issue would be minor.

The ESCs noted that pembrolizumab is used to treat other cancers without reference to PD-L1 status, including melanoma, Hodgkin’s lymphoma and urothelial carcinoma. The ESCs accepted the applicant’s argument that PD-L1 is over-expressed in more than 87% of patients with Hodgkin’s lymphoma. As such, the ESCs considered that treating these patients without testing PD-L1 levels would be reasonable. However, the ESCs noted that, when a 5% TPS threshold was used as the cut-point, 62% of chronic sun-damaged melanoma patients, 33% of invasive primary urothelial carcinoma patients and 49–60% of NSCLC patients were

classified PD-L1 positive. Despite this, testing of PD-L1 status is required in NSCLC patients, but not in melanoma and urothelial carcinoma patients prior to treatment with pembrolizumab.

The ESCs noted that information on the significance of different histotypes, particularly squamous histology, had not been addressed.

The ESCs queried whether the MBS fee for PD-L1 testing should be lower than the \$74.50 proposed. The applicant argued that this fee is consistent with MBS item 72848 which is for IHC examination of biopsy material for one, two or three of the oestrogen, progesterone and HER2 antibodies. The ESCs noted that the MBS fee for item 72846 which covers IHC examination of biopsy material for one, two or three of any of the other antibodies is \$59.60. The ESCs noted that as PD-L1 testing only involves IHC examination of one antibody, the lower fee may be more appropriate.

The ESCs noted that two testing scenarios were modelled. In the first, testing occurred at diagnosis of NSCLC. In the second, 30% of patients were re-biopsied and re-tested once they progressed to stage IV disease (using 1 year mortality rates). The ESCs considered that, while decisions on when to test impacted upon the economic estimates, the impact of adding in costs for re-biopsy was small.

The ESCs noted that the rate of biopsy-related adverse events had been reduced from 22% to the 14% figure previously recommended by MSAC when calculating MBS costs ([MSAC Public Summary Document Application 1161, November 2012](#)). The ESCs noted that MBS costs of disease management and drug administration, and re-biopsy in patients who progress to stage IV disease in the prevalent population, had not been included in the financial estimates, beyond Year 1. As such, the ESCs considered that the MBS costs could be higher than estimated.

15. Other significant factors

Nil

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

MSD is pleased that MSAC have foreshadowed their support for PD-L1 testing as this is a critical step to enable appropriate 1L NSCLC patients access to pembrolizumab.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)