



Australian Government

Department of Health

MEDICAL SERVICES ADVISORY COMMITTEE

PD-L1 immunohistochemistry testing for access to pembrolizumab for the treatment of locally advanced or metastatic non-small cell lung cancer

Protocol 1440

October 2016

Purpose of application

This application is requesting a Medicare Benefits Schedule (MBS) listing for testing of Programmed Death 1 Ligand (PD-L1) expression in advanced non-small cell lung cancer (NSCLC). This listing is required to support an integrated co-dependent submission for use of the PD-L1 test to determine eligibility for pembrolizumab in first line treatment of NSCLC.

A protocol (No. 1414) has already been ratified to determine eligibility to pembrolizumab in the second line setting. Table 1 outlines the differences between this protocol (No. 1440) and Protocol 1414.

Table 1 Comparison of Protocol 1414 and Protocol 1440

Population and medical condition eligible for the proposed medical service	
Background on non small cell lung cancer	Same as Application 1414
Role of Programmed Death-1 pathway as a therapeutic target in cancer	Same as Application 1414
Testing for PD-L1 expression	
Prevalence and prognostic value of PD-L1 expression in NSCLC	
Proposed patient population	New information for Application 1440
Evidence for the proposed patient population	New information for Application 1440
KN001	
KN024	
KN042	New information for Application 1440
Intervention – proposed medical service	
Description of proposed medical service	Same as Application 1414
Proposed MBS listing	Same as Application 1414
Expected utilisation	
Reference standard	New information for Application 1440
Delivery of the proposed medical test	
Where, by whom, frequency of testing	Same as Application 1414
Co-dependent information	
Co-dependent drug	New information for Application 1440
Comparator	
Test	New information for Application 1440
Drug	New information for Application 1440
Co-dependence	New information for Application 1440
Clinical claim for proposed medical service	
PD-L1 test outcomes	New information for Application 1440
Drug Outcomes	Same as application 1414
Risk to the patient	New information for Application 1440
Type of economic evaluation	New information for Application 1440
Fee for the proposed medical service	
Proposed funding	Same as application 1414
Direct costs of equipment/resources used with the service	Same as application 1414
The proposed fee	Same as application 1414
Clinical Management Algorithm - clinical place for the proposed intervention	
Current treatment algorithm	New information for Application 1440
Future treatment algorithm	New information for Application 1440
Regulatory Information	
Decision analytic	New information for Application 1440
Healthcare Resource use	New information for Application 1440
Question for public funding	New information for Application 1440

As the biomarker aspects of this protocol are largely unchanged compared to those ratified through Protocol 1414, the sponsor proposes that a streamlined review process is undertaken by PASC.

Population and medical condition eligible for the proposed medical services

Non-small cell lung cancer

Lung cancer is the 5th most commonly diagnosed cancer, with over 10,000 patients diagnosed each year, and a prevalence of around 94 people per 100,000.¹ In 2014, lung cancer was the most common cause of cancer death, accounting for 18.9% of all cancer deaths (8,630 deaths).² Non-small cell lung cancer (NSCLC) accounts for approximately 66% of all lung cancer cases³. Progress has been made in the clinical management of early stage NSCLC. However, the prognosis for advanced disease has not improved substantially. With an overall 5-year survival rate of 13-16%, the treatment of NSCLC remains a high unmet medical need⁴.

Role of the Programmed Death-1 pathway as a therapeutic target in cancer

In recent years, it has become apparent that cancers are recognized by human immune system and that under certain circumstances the immune system can obliterate tumours. Recently, the PD-1 pathway has emerged as a major immune checkpoint by which tumours suppress lymphocyte function. This pathway consists of PD-1, a protein expressed on activated immune cell types such as T cells and B cells, and its ligands, PD-L1 and PD-L2 which are expressed on many tumours. Cancer cells drive high expression levels of PD-L1 on their surface, allowing activation of the inhibitory PD-1 receptor on any T cells that infiltrate the tumour microenvironment, effectively switching those cells off. Indeed, up-regulation of PD-L1 expression levels has been demonstrated in many different cancer types (eg, melanoma [40%-100%], NSCLC [35%-95%], and multiple myeloma [93%]), and high levels of PD-L1 expression have been linked to poor clinical outcomes (Hino et al, 2010, Wang et al, 2011, Dong et al, 2002, Konishi et al, 2004, Liu et al, 2007, Patel et al, 2015).

It has been proposed that immunotherapy targeting this pathway may be a potential cancer treatment modality. Hence several molecules targeting this pathway are currently under clinical development in NSCLC. One such molecule is pembrolizumab.

Pembrolizumab mechanism of action

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) designed to target the programmed death-1 receptor and thus directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumour regression and ultimately immune rejection. Pembrolizumab only potentiates existing immune responses in the presence of antigen and does not non-specifically activate T cells.

Evidence shows that PD-L1 expression levels correlate with increased response to pembrolizumab. For instance, in NSCLC phase 1 clinical trial data showed a correlation between PD-L1 expression and

¹ Lung Foundation: Lung Disease in Australia [accessed 7th May 2015]

² Cancer in Australia: an overview 2014, AIHW, Table 7.2, Pg 49 of document, [AIHW Cancer in Australia an overview](#) [accessed 7th May 2015]

³ Lung cancer in Australia: an overview, AIHW, [AIHW Lung cancer in Australia an overview](#) Table 3.8, Pg 24 [accessed 7th May 2015]

⁴ Lung cancer in Australia: an overview, AIHW, [AIHW Lung cancer in Australia an overview](#) Figure 5.2, Pg 65 [accessed 7th May 2015]

response to pembrolizumab, supporting the role of PD-L1 expression testing as a predictive biomarker (Garon et al, 2015).

Testing for PD-L1 expression

PD-L1 expression in NSCLC tumour biopsies can be assessed using immunohistochemical (IHC) testing with antibodies that bind specifically to the PD-L1 protein.

Three PD-L1 assays have been used during the pembrolizumab NSCLC clinical development program:

- A Prototype Research Assay (PRA).
- A Clinical Trial Assay (CTA).
- The PD-L1 22C3 pharmDx Market Ready Assay (MRA).

All of these assays tests use the same antibody (mouse anti-human monoclonal antibody clone 22C3). However the associated kit reagents are slightly different

The Clinical Trial Assay and the Market Ready Assay were both developed by Dako, the company with whom MSD are partnering for development of the companion diagnostic.

Prevalence and prognostic value of PD-L1 expression in NSCLC

As PD-L1 is a relatively new biomarker, there is limited data on the prevalence and prognostic role of PD-L1 expression in NSCLC. Whilst earlier studies have given rise to mixed results, two recent meta-analyses have shown that positive PD-L1 expression is correlated with poor prognosis in NSCLC patients (Wang et al, 2015; Zhou et al, 2015).

Zhou et al, 2015 also found that PD-L1 expression is not related to gender, histology type, smoking status, tumor stage, or the absence or presence of lymph node metastasis. The relationship between PD-L1 expression and other biomarkers such as KRAS, EGRF and ALK has yet to be determined. Whilst some studies have associated PD-L1 positive status with the presence of KRAS and EGFR mutation, this finding has been inconsistent (Ji et al, 2015).

In terms of PD-L1 prevalence, early screening data from multinational clinical trials (including Australia) that MSD is undertaking has found that approximately 61% of advanced NSCLC patients screened are PD-L1 positive ($\geq 1\%$ PD-L1 expression) and that approximately 23% of patients are strongly positive ($\geq 50\%$ PD-L1 expression) (Garon et al, 2015). MSD is committed to providing an overview of the prevalence and prognostic data for PD-L1 in NSCLC as part of co-dependent submission.

Proposed patient population

As proposed in Application 1414, the patient population which would benefit from PD-L1 testing are diagnosed NSCLC patients (squamous, non squamous and not otherwise specified) of all disease stages.. The outcome of this test will determine whether the patients are eligible for subsequent treatment with pembrolizumab. Eligible patients for pembrolizumab will be stage IV NSCLC and may have either high expression of PD-L1 $\geq 50\%$ staining (as per the KN024 trial described in the Clinical Evidence Section) or PD-L1 expression $\geq 1\%$ staining (as per KN042). This protocol covers both situations.

In the co-dependent technology submission MSD will present data on intra-block and intra-case heterogeneity for PD-L1 expression in NSCLC. MSD also commits to reviewing the literature for

additional publicly available evidence on tissue heterogeneity with respect to PD-L1 expression in NSCLC and with regard to the role of irradiation on PD-L1 expression.

Clinical evidence for the predictive role of PD_L1

Keynote 001

The role of PD-L1 testing in predicting patient response to pembrolizumab in locally advanced/metastatic NSCLC was identified in Keynote 001 (KN001), an adaptive phase 1 trial (Garon et al, 2015).

The objectives of KN001 were to assess the efficacy and safety of pembrolizumab in patients with advanced NSCLC, and to define and validate an expression level of PD-L1 that is associated with the likelihood of clinical benefit. Key characteristics of the KN001 trial are outlined in Table 2.

Table 2 Trial design for Keynote 001

Trial	Patient population	Study design	Sample Size and Endpoints
Keynote 001	<ul style="list-style-type: none"> Part C: NSCLC of any histology Part F: NSCLC with PD-L1 protein expression Mix of treatment naïve and progressive disease following 1 or two treatments 	Open label phase 1 <ul style="list-style-type: none"> 10 mg/kg Q3W Pembrolizumab 10 mg/kg Q2W Pembrolizumab 2 mg/kg Q3W Pembrolizumab 	Part C N=38 Part F N=457 Primary endpoint <ul style="list-style-type: none"> Response rate as per RECIST 1.1 No. of pts experiencing adverse events No. of pts experiencing dose-limiting toxicities

Note: a full explanation of the design and results can be found in Garon et al, 2015.

Early results (Part C) of KN001 showed that pembrolizumab had clinical activity in subjects with NSCLC (Gandhi et al, 2014). Moreover, a greater clinical benefit from pembrolizumab treatment appeared to be associated with a higher level of PD-L1 expression.

On the basis of these results, amendments were made to the KN001 trial protocol to further explore this relationship (Part F). In particular, part F focussed on defining and validating an expression level of PD-L1 associated with a greater likelihood of clinical benefit.

Biomarker analysis in KN001

All three PD-L1 assays (PRA, CTA and MRA), using the 22C3 antibody, were used in the KN001 trial:

- The PRA was used to screen patients for eligibility to KN001 Part C and Part F. It is no longer in use.
- The CTA was used for biomarker cut point determination and assessment of PD-L1 expression during biomarker validation.
- The MRA was used for retrospective scoring of the Biomarker Validation subjects as part of the efficacy analysis in KN001 Part F.

Biomarker analysis to determine patient eligibility to KN001

All patients enrolled in the KN001 trial were to have been deemed positive for PD-L1 expression ($\geq 1\%$) using the Prototype Research Assay. Testing was to be performed on a contemporaneous biopsy sample if possible. This meant that either the sample needed to be collected within 60 days of the first dose of pembrolizumab or the sample needed to be collected in the time between the last dose of the previous systemic anticancer therapy and the first dose of pembrolizumab. Archival tissue was analysed when contemporaneous tissue were not available.

PD-L1 expression cut point selection and scoring system

Overall, 182 patients from KN001 were assigned to a group to define a PD-L1 cut off.

Key points of this assessment are:

- 129 patients had measureable disease (RECIST criteria) and samples that could be evaluated for PD-L1 expression
- PD-L1 expression was assessed using the Clinical Trial Assay
- Contemporaneous biopsy specimens (≤ 60 days old) were predominantly used, although archival tissue was analysed when contemporaneous tissue were not available (n=25 archival samples)

Receiver operating characteristic (ROC) analysis was employed to develop a PD-L1 expression scoring system and to define potential PD-L1 cut points which were associated with an enhanced response to pembrolizumab.

ROC analysis was performed on the following immunohistochemistry (IHC) scoring methods:

- **Proportion score (PS):** defined as the percentage of cells with membranous PD-L1 staining at any intensity
- **Proportion score 2+ or 3+ (P2S):** defined as the percentage of cells with membranous PDL1 staining at moderate (2+) or strong (3+) intensity
- **Proportion score 3+ (P3S):** defined as the percentage of cells with membranous PD-L1 staining at strong intensity (3+)
- **Modified H-score (HS):** which provides a numerical value that accounts for the proportion of cells staining for PD-L1 at each of the 3 intensities.

The results of the ROC analyses are presented in Figure 1.

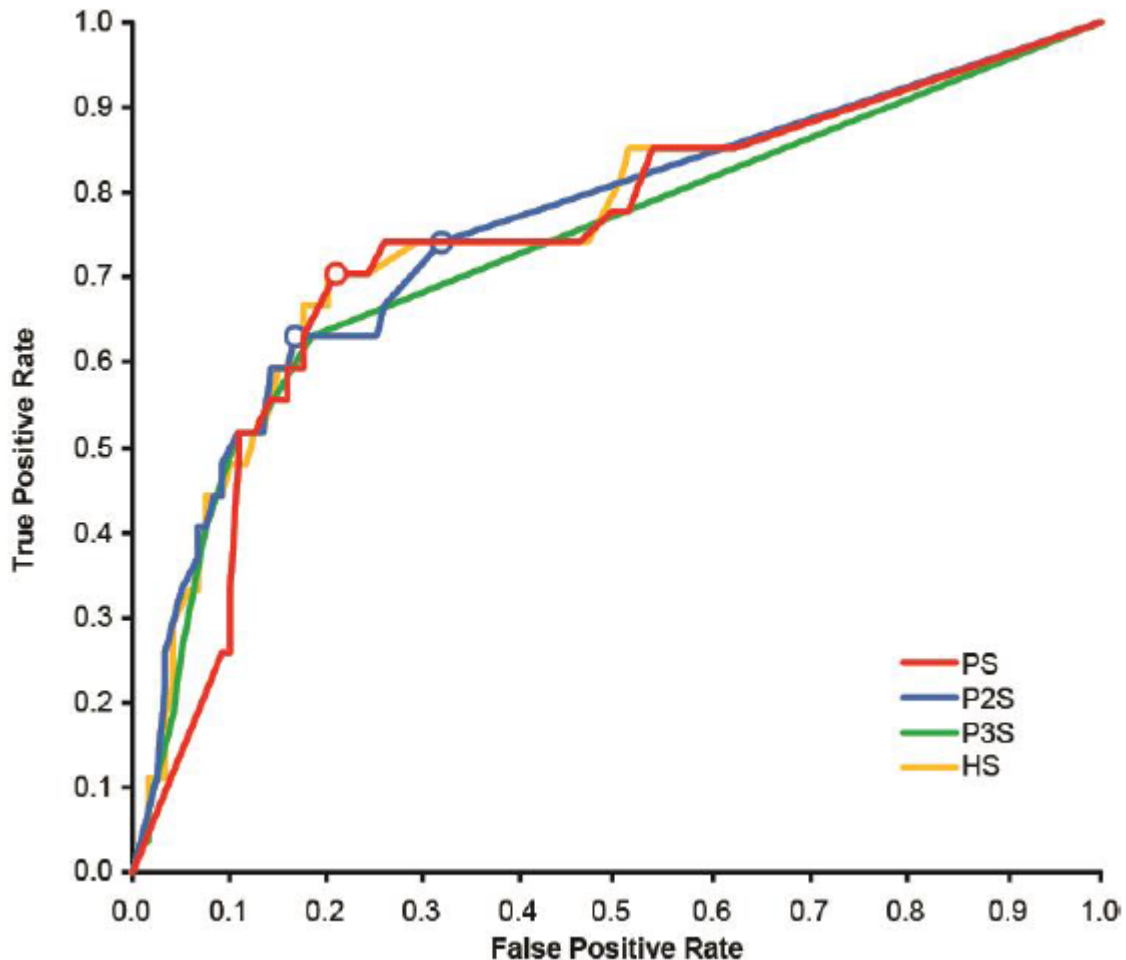


Figure 1 Receiver operating characteristic analysis based on investigator-assessed immune-related response criteria (irRC) and membranous PD-L1 expression.

Source: Figure S.3 (p.10) of Supplement to Garon et al (2015)

The open circle on the PS curve represents the point at which Youden's J statistic (Youden's Index) is maximised for the ROC curve assessing PD-L1 expression defined as the proportion of cells with membranous PD-L1 staining at any intensity. This point corresponds to a cut point of membranous PD-L1 expression of any intensity in 45-50% of tumour cells.

No major differences were observed in ROC area under the curve for the potential scoring methods, regardless of the approach used (Figure 1). The positive predictive value of the Clinical Trial Assay was not improved by incorporating PD-L1 expression on inflammatory T cells.

Hence, membranous PD-L1 expression in at least 50% of tumor cells (proportion score, $\geq 50\%$) was selected as the PD-L1 strong vs weak cut point on the basis of the ease of use and ROC analysis

Biomarker validation of PD-L1 expression

Following biomarker cut point selection, an analysis of the anti-tumour activity of pembrolizumab according to PD-L1 expression level was performed on a subset of patients enrolled in KN001. This group included 313 patients (223 previously treated; 90 previously untreated), and PD-L1 status was measurable in 230 patients.

Key points of this assessment were:

- All PD-L1 testing was performed using the Clinical Trial Assay.
- Scoring was also done retrospectively using the Market Ready Assay and results were identical to the Clinical Trial Assay results
- When archival tissue was used, slides must have been sectioned within 6 months of performing PD-L1 testing due to antigen degradation.
- PD-L1 scoring was reported as based on following categories:
 - Percentage of neoplastic cells with PD-L1 staining of <1% (PS <1%)
 - Percentage of neoplastic cells with PD-L1 staining between 1-49% (PS 1 - 49%)
 - Percentage of neoplastic cells with PD-L1 staining \geq 50% (PS \geq 50%)

The results of this analysis showed that the response rate to pembrolizumab was increased in patients with higher levels of PD-L1 expression (Garon et al, 2015).

Keynote -010

The clinical utility of the PD-L1 test was confirmed in the Keynote 010 trial. This trial compared the efficacy of pembrolizumab to docetaxel in PD-L1+ patients who had failed platinum-based chemotherapy. It showed that overall survival benefit was greater in patients who expressed higher levels of PD-L1 (\geq 50%) compared to those expressing lower levels (\geq 1-49%) (Herbst et al, 2015).

Table 3 Clinical utility of the PD-L1 test in the Keynote 010 trial

PD-L1 tumour proportion score	n/N	HR (95% CI)
\geq 50%	204/442	0.53 (0.40-0.70)
1-49%	317/591	0.76 (0.60-0.96)

Keynote -024

Data from KN024 will represent the pivotal evidence presented in MSD's co-dependent submission to support listing of pembrolizumab as a 1st line therapy in patients with NSCLC.

Keynote 024 is a prospective randomised controlled trial designed to assess the efficacy and safety of pembrolizumab monotherapy compared to investigator's choice of platinum-based chemotherapies in subjects previously untreated for Stage IV non-small cell lung cancer, whose tumours strongly express PD-L1 (\geq 50% positive) and are EGFR wild type and ALK translocation negative.

PD-L1 expression was determined using the Market Ready Assay .

Key characteristics of the KN024 trial are outlined in Table 4.

Table 4 Trial design for KN024

Trial	Patient population	Study design	Sample Size and Endpoints
Keynote 024	<ul style="list-style-type: none"> • PD-L1 strong positive Stage IV NSCLC (≥50%) • No prior therapy • EGFR wild-type and ALK negative 	<p>Multi-centre, multi-country, Phase II/III Randomized (1:1)</p> <ul style="list-style-type: none"> • 200 mg Q3W pembrolizumab • Platinum-based chemotherapy Investigators choice of cisplatin/carboplatin + pemetrexed (non-squamous only with or without pemetrexed maintenance); cisplatin/carboplatin +gemcitabine; paclitaxel + gemcitabine (with or without pemetrexed maintenance) <p>Control patients offered pembrolizumab following progression</p>	<p>N=300 Primary endpoint:</p> <ul style="list-style-type: none"> • PFS • Key safety <p>Other endpoints</p> <ul style="list-style-type: none"> • OS • ORR • EORTC QLQ-C30 and EORTC QLQ LC-13, • EQ-5D 3L

Abbreviations: Q3W = every 3 weeks; OS= overall survival; PFS = progression free survival; SQ = squamous; NSQ = nonsquamous; IRC = independent Review Committee

Keynote -042

KN042 is another study investigating use of pembrolizumab as a 1st line therapy in NSCLC patients whose tumours are PD-L1 positive (≥1% positive), EGFR wild type and ALK translocation negative. Evidence from this study could inform a co-dependent submission in the future.

Table 5 Trial design for KN042

Trial	Patient population	Study design	Sample Size and Endpoints
Keynote 042	<ul style="list-style-type: none"> • PD-L1+ (≥1%) Stage IV NSCLC • No prior therapy 	<p>Multi-centre, multi-country, Phase II/III Randomized (1:1)</p> <ul style="list-style-type: none"> • 200 mg Q3W pembrolizumab • Platinum-based chemotherapy investigators choice of carboplatin + paclitaxel with or without pemetrexed maintenance for nonsquamous patients; carboplatin + pemetrexed with or without pemetrexed maintenance for nonsquamous patients. 	<p>N=1240 Primary endpoint:</p> <ul style="list-style-type: none"> • OS <p>Other endpoints:</p> <ul style="list-style-type: none"> • PFS • Key safety

Abbreviations: Q3W = every 3 weeks; OS= overall survival; PFS = progression free survival; SQ = squamous; NSQ = nonsquamous; IRC = independent Review Committee

Prerequisites to biomarker analysis in KN024 and KN042

Key features of the biopsy material used to assess for PD-L1 status were:

- Biopsy of a tumour lesion must have been undertaken either at the time of or after the diagnosis of metastatic disease has been made AND from a site not previously irradiated.
- Core needle or excisional biopsies, or resected tissue were required. Any cytology specimens including fine needle aspirate (FNA), endobronchial ultrasound (EBUS) or cell blocks were not acceptable
- Biopsy specimens could come from either a primary tumour or a metastatic lesion.
- Sufficient biopsy material was required for biomarker analysis. A biopsy length of 0.3-0.5 cm was recommended. The PD-L1 test required a sample of 4-5 microns.

As KN024 and KN042 studies contain histology samples only, MSD will commit to determine whether there is evidence available, regarding PD-L1 testing on cytology samples.

The sponsor will also include a review of available information on pembrolizumab response according to histological subtype (squamous versus nonsquamous) in the co-dependent technology submission. Scoring of the PD-L1 test.

Based on the analyses undertaken in KN001, the following scoring approach was used in KN024:

- Scoring was undertaken using a proportional approach.
- From a histology sample, at least 100 evaluable tumour cells are scored.
- Positive staining is defined as complete or partial staining of the cell membrane. Any intensity of staining is acceptable.
- The proportion of cells that are positive is the outcome of the scoring.
- Negative staining is defined as no staining of plasma membrane.
- Granular staining in the cytoplasm is not considered to be positive staining.

In the co-dependent technology submission, MSD will commit to including data on the reproducibility of PD-L1 scoring between pathologists.

Intervention – proposed medical service

Description of proposed medical service

The Market Ready Assay (PD-L1 22C3 pharmDx assay) will be made commercially available in Australia. TGA registration of the Market Ready Assay, including any applicable registered trademark, is being undertaken by Dako. Registration is pending but is scheduled to be completed prior to consideration of the co-dependent technology submission by MSAC.

Proposed MBS listing

In light of the co-dependency issues between PD-L1 testing on NSCLC tumours and treatment with pembrolizumab, MSD has received advice from the Department that a new MBS item number should be used as a placeholder through the assessment process. This arrangement provides MSAC with the flexibility to recommend a new MBS item number be created specifically for PD-L1 testing associated with access to pembrolizumab, should they deem it necessary.

Table 6 Proposed MBS Item Descriptor

Category 6 – Pathology Services
MBS item number

Immunohistochemical examination of biopsy material by immunoperoxidase or other labelled antibody techniques using a PD-L1 antibody to determine if the requirements relating to programmed cell death ligand 1 (PD-L1) status for access pembrolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled
Fee: To be determined **Benefit:** To be determined

This proposed MBS listing is the same as that nominated in Protocol 1414, i.e. the same MBS item number would be used to test for PD-L1 expression, regardless of whether this is to determine eligibility to pembrolizumab in the first or later lines of therapy.

The sponsor notes that the proposed item descriptor and fee may be updated and aligned with Application 1414, following its consideration by MSAC

MSD commits to aligning the definition of biopsy with the conclusions from the literature search identified above.

Expected utilisation

An estimate of the size of the testing population is provided below. The proposed incidence of NSCLC is comparable to that determined by the Assessment group for ALK testing and accepted by the Department of Health³. Given that the preferred clinical place in therapy of the PD-L1 test is at time of initial diagnosis (see Clinical Management Algorithm section), the co-dependent submission subject of this protocol is not expected to result in a change in utilisation of the test, relative to that nominated in Protocol 1414.

Table 7 Incidence of NSCLC

No. of patients including all lung cancers (2014)	11,580 ¹
Incidence of all NSCLC	66% (based on 2002-2007) ²
Eligible patient pool for PD-L1 testing	7,643

¹Cancer in Australia: an overview 2014, AIHW, Table 3.2 Pg 17 of document, [Cancer in Australia: an overview 2014, AIHW](#) [accessed May 5 2015]

²Lung cancer in Australia: an overview, AIHW, [Lung cancer in Australia: an overview, AIHW](#) Pg 24

³1250-ALK-Final DAP-Accessible, Pg 8 of document

Reference standard

Currently, there is no established evidentiary standard for PD-L1 testing.

As the Market Ready was used to determine eligibility for enrolment in the KN024 and KN042 trials, MSD nominates the Market Ready Assay as the evidentiary standard for PD-L1 expression testing associated with pembrolizumab treatment.

Delivery of proposed medical test

Where service would be delivered

As IHC is a common procedure in histopathology laboratories and as PD-L1 expression is anticipated to be identified frequently (in approx. 61% of cases for $\geq 1\%$ PD-L1 expression; 23% for $\geq 50\%$ PD-L1

expression (Garon et al, 2015), it is proposed that PD-L1 IHC testing be eligible to be carried out in any pathology laboratory holding the appropriate accreditation to claim pathology services through the MBS.

In practice, it is anticipated that the majority of PD-L1 testing would occur in pathology laboratories associated with a public hospital and PD-L1 testing of outpatient samples would be tested in private pathology laboratories .

Consistent with introduction of diagnostic tests associated with access to other targeted therapies, pathologist training and quality assurance programs would be expected to be developed with respect to delivery of diagnostic tests for access to treatments targeting the PD-1 pathway on the PBS.

By whom

A certified pathologist would be responsible for conducting the test and reporting the results.

Frequency of testing

Patients would require only 1 PD-L1 test through the course of their disease. The test should be undertaken prior to commencement of pembrolizumab to enable identification of those patients most likely to benefit from treatment. Potential options regarding the clinical place in therapy of the PD-L1 test are outlined in the section entitled **Clinical Management Algorithm**.

There is no known role for PD-L1 testing in monitoring a patient's response to pembrolizumab treatment.

Co-dependent information

Co-dependent drug

Pembrolizumab is the co-dependent pharmaceutical medicine.

In line with the clinical trial data from KN024, the initial application will propose reimbursement of pembrolizumab for treatment naïve Stage IV NSCLC patients whose tumours are EGFR wild type and ALK translocation negative, and have a high expression of PD-L1 ($\geq 50\%$ staining).

A further submission could be lodged in the future in line with the clinical trial data from KN042. This submission would propose to change the reimbursement criteria for pembrolizumab to allow use in treatment naïve Stage IV NSCLC patients whose tumours are EGFR wild type and ALK translocation negative, and express PD-L1 regardless of level of expression ($\geq 1\%$ staining).

Comparator

Test

Given that the evidentiary standard and the test to be used in clinical practice are the same, unlike Protocol 1414, no comparison of PD-L1 assays (e.g. Clinical Trial Assay and Market Ready assay) is needed for the purposes of this submission.

As a supplementary comparison, it is proposed that an assessment of comparative assay performance of the Market ready assay and other tests used to predict response to anti-PD-L1 therapies (including, but not limited to, other commercially available PD-L1 antibodies/assays) will be

presented in the submission. This assessment will also consider alternative cut points used for alternative PD-L1 tests.

Drug

In treatment naïve patients with metastatic NSCLC whose tumours are EGFR wild type, ALK translocation negative, platinum-based therapy such as carboplatin + gemcitabine is the most frequently used treatment option. Pemetrexed maintenance may also be used in nonsquamous NSCLC patients who respond to chemotherapy.

DRAFT

Co-dependence

It is proposed that the MSAC submission presents efficacy, safety and cost effectiveness comparisons of PD-L1 testing and pembrolizumab with

- No PD-L1 testing and management with platinum-based therapy
- No PD-L1 testing and management with pembrolizumab

Clinical claim for the proposed medical service

The hypothesis being tested in the KN024 and KN042 clinical trials is that PD-L1 testing followed by pembrolizumab as a first line treatment in patients with metastatic NSCLC whose tumours are EGFR wild type and ALK translocation negative and express PD-L1 ($\geq 1\%$ and $\geq 50\%$) is associated with improved health outcomes. It will be driven by two factors:

1. Acceptable safety and analytical performance of PD-L1 test (to be assessed by MSAC).
2. Superior effectiveness with acceptable safety of treating PD-L1 positive patients with pembrolizumab relative to standard of care (to be assessed by PBAC).
3. Acceptable clinical utility of the PD-L1 test

Expected health outcomes relating to the medical service

PD-L1 Test Outcomes

Outcome measures suitable to assess the analytic performance of PD-L1 IHC testing include:

- Sensitivity
- Specificity
- Positive Predictive Value
- Negative Predictive Value
- Receiver Operating Characteristic (ROC)

Measures of comparative performance of PD-L1 testing methods:

- Rates of re-testing
- Concordance with other commercially available PD-L1 antibodies
- Comparison with other assays for determining response to anti-PD-L1 treatment, if available

Measure of Clinical Utility of PD-L1 test

- Outcomes with pembrolizumab treatment with and without PD-L1 testing

Other considerations

- Rates of re-biopsy
- Anticipated test turnaround time
- The estimated number of patients being tested
- The number of patients tested per case of PD-L1 positive ($\geq 1\%$ and $\geq 50\%$) result detected

- The number of patients tested per case of PD-L1 positive ($\geq 1\%$ and $\geq 50\%$) result treated with pembrolizumab
- The cost of testing per case of PD-L1 positive ($\geq 1\%$ and $\geq 50\%$) NSCLC detected
- The cost of testing per case of PD-L1 positive ($\geq 1\%$ and $\geq 50\%$) NSCLC treated with pembrolizumab.

Drug Outcomes

Measures of clinical efficacy for pembrolizumab include:

Primary outcome:

- Overall survival
- Progression free survival
- Safety and tolerability

Secondary outcomes

- Objective tumour response rates (complete response or partial response according to RECIST and irRC criteria)
- Quality of life
- Disease control rate (response rate + rate of stable disease)
- Duration of response
- Rate of disease progression
- Time to progression

Risks to patient

PD-L1 testing is performed on tissue slices taken from a biopsy specimen obtained as part of standard diagnostic work-up and thus, in itself, does not incur any risks to patient.

The main risk to patient would occur if a re-biopsy is required in order to obtain tissue to perform the IHC test. Re-biopsies can result in complications such as pneumothorax and haemorrhage. These complications are considered to occur in 14% of cases⁵. A re-biopsy would be required if insufficient tissue is retrieved from the initial biopsy to undertake the desired biomarker tests.

However, it is unlikely that the re-biopsy would be required specifically to undertake PD-L1 testing alone as IHC only uses a small amount of tissue (one 4 micron section, compared to approximately 50 microns for EGFR testing). Instead the re-biopsy would be required to undertake all biomarker tests relevant to the patient. Hence, introduction of this test is not expected to result in an increase in re-biopsy rates.

Type of economic evaluation

As KN024 and KN042 are designed as superiority trials, it is anticipated that a cost-utility evaluation will be presented.

⁵ Pg 7 1161-FinalPSD-Aug2013 Gefitinib first line testing for mutations of epidermal growth factor receptor (EGFR) in patients with metastatic non-small cell lung cancer (NSCLC)

Fee for the proposed medical service

Proposed funding

It is proposed that PD-L1 testing should be a “pathologist determinable test”, in line with all other IHC tests.

Direct costs of equipment/resources used with service

IHC testing is a well established technique in all major pathology labs. Laboratories already have the platform infrastructure and reagents to perform PD-L1 IHC testing. The PD-L1 antibody is the only additional resource required.

The proposed fee

The final fee request has yet to be determined. It is expected to be consistent with other fees for immunohistochemistry and will be based on consideration of the capital and the labour components required for pathologists to undertake PD-L1 testing and interpret and report the results.

Clinical Management Algorithm - clinical place for the proposed intervention

Current treatment algorithm

The current treatment algorithm is outlined in Figure 1. After histological confirmation of NSCLC, biomarker tests are conducted (for EGFR and ALK) on all nonsquamous and NOS (not otherwise specified) patients. If the patient has Stage IV NSCLC, these tests determine first line treatment. If the tumour is EGFR mutant or ALK translocation positive, patients are treated with targeted therapy first (erlotinib/gefitinib for EGFR and crizotinib for ALK). All other patients (non-squamous patients who are EGFR wild type or ALK translocation negative and those with squamous histology) will be treated with a platinum doublet (e.g. carboplatin + gemcitabine) as the initial therapy. Pemetrexed is used as a first line maintenance therapy for some non-squamous patients without progressive disease.

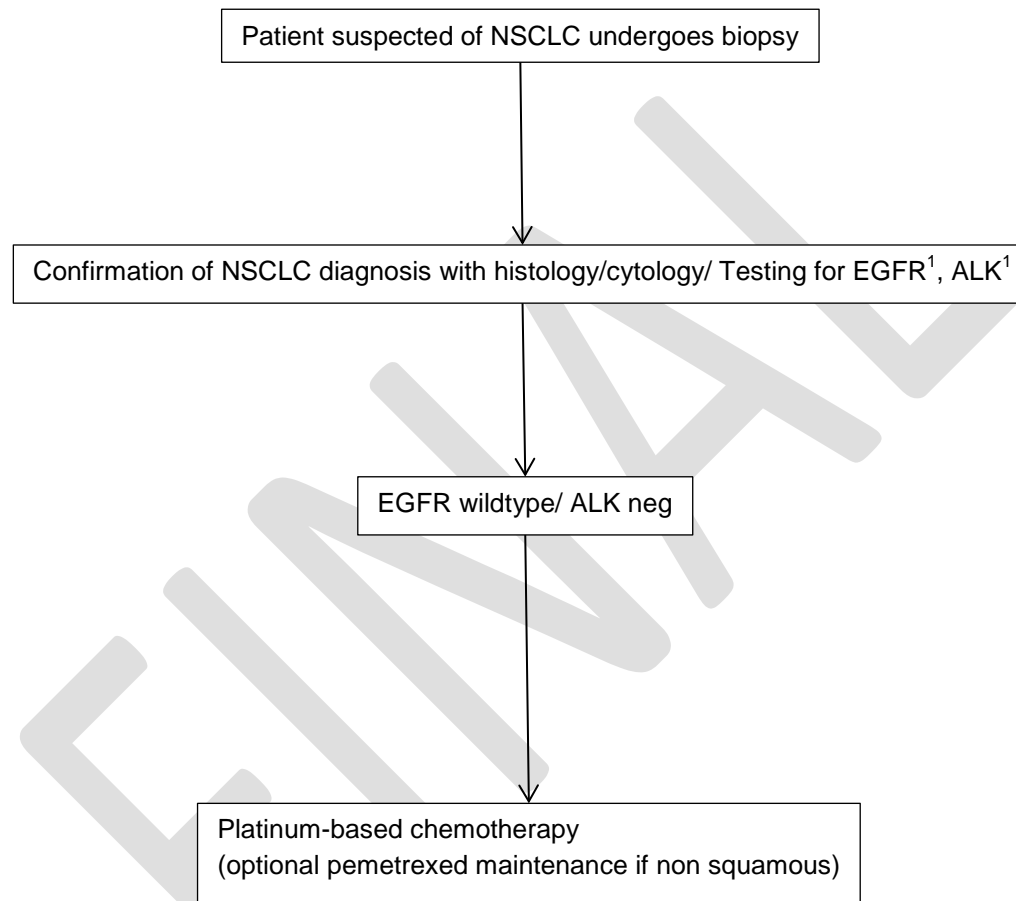
As the co-dependent technology submission associated with Application 1414 proposes that the PD-L1 test be undertaken as part of the initial diagnostic workup of a NSCLC patient, there will be no change required to the placement of the test with Application 1440, should this be approved.

Future treatment algorithms

The sponsor proposes that PD-L1 testing is undertaken in both squamous and nonsquamous tumours on recently cut (within 6 months) sections from initial biopsy of all NSCLC patients, regardless of the stage of the disease. It should be performed at the time of other biomarker assessments, i.e. PD-L1 IHC could be done alongside ALK IHC and other diagnostic IHC tests and in parallel to EGFR testing (Figure 2) and undertaken in patients with Stage IV NSCLC. From a practical perspective in this scenario, sections for all testing would be cut at the same time. IHC testing would be performed on the first lot of sections with the residual sections sent away for EGFR testing. This scenario has support from pathologists and oncologists as the most efficient and useful place for testing. Patients whose tumours express PD-L1 (either $\geq 1\%$ or $\geq 50\%$) and are EGFR wild type and

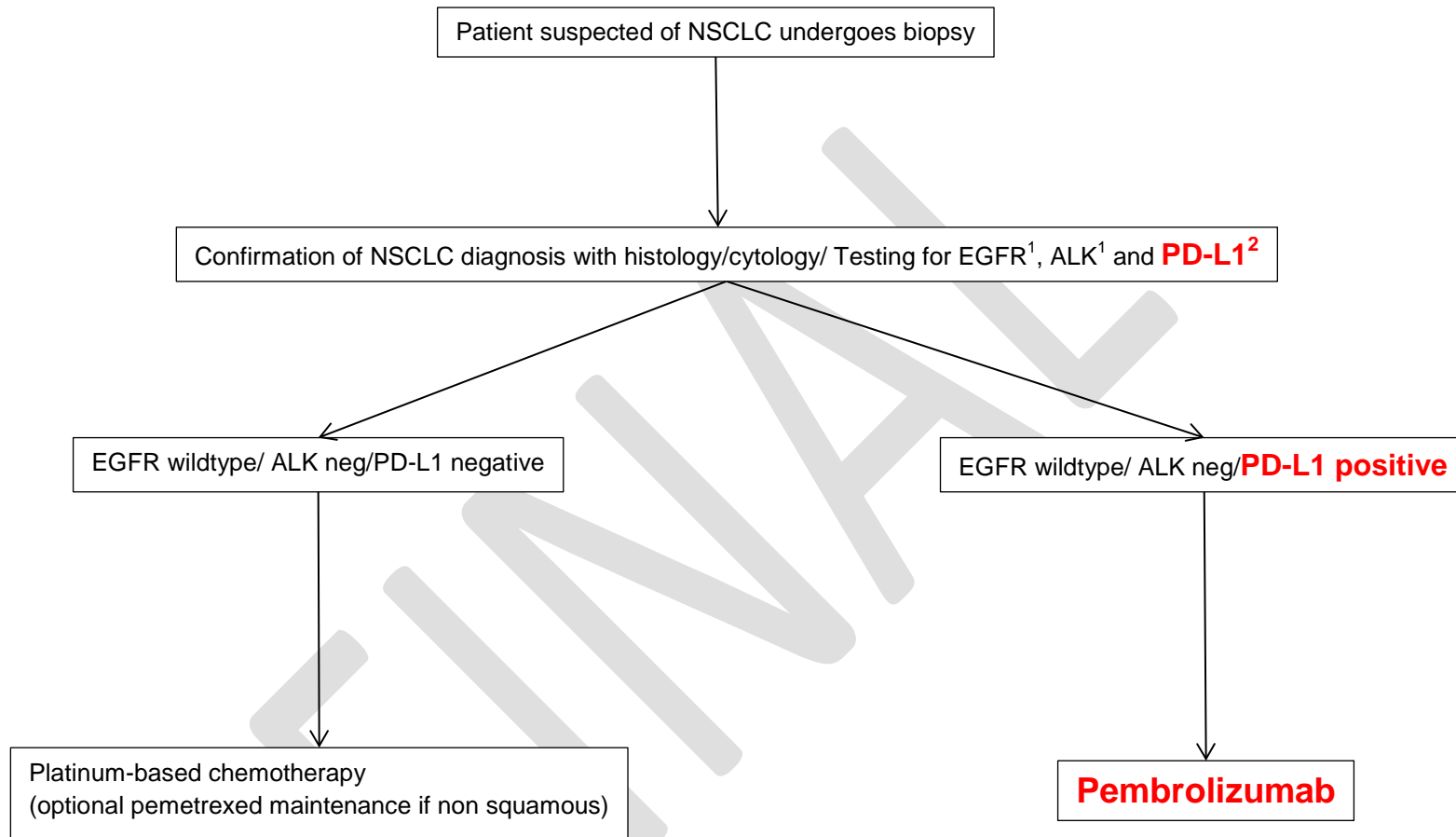
ALK translocation negative will be treated with pembrolizumab instead of platinum-based therapy in accordance with the PBS criteria accepted by the PBAC.

FINAL



¹ non squamous or NOS histologies only

Figure 2 Current treatment algorithm



¹ non squamous or NOS histologies only
² All histologies if stage IV

Figure 3 Treatment algorithm showing PD-L1 testing and subsequent treatment with pembrolizumab

Regulatory Information

Regarding the PD-L1 testing, the regulatory process will be managed by Dako. Regulatory approval of the PD-L1 test is expected prior to MSAC consideration of this co-dependent technology submission.

In the future, MSD anticipates filing a TGA submission for pembrolizumab in treatment naïve patients with NSCLC whose tumours express PD-L1 and are EGFR wildtype and ALK translocation negative

Decision analytic

An assessment of the cost-effectiveness of introducing PD-L1 testing to determine patient eligibility to pembrolizumab should take into account the parameters outlined in Table 8, Table 9 and Table 7

F E M I N A L

Table 8 Summary of PICO to define research question

PICO	Comments
Patients	Patients with EGFR wild type and ALK negative non-small cell lung cancer who have had no prior treatment, and whose tumours express PD-L1 ($\geq 50\%$ and $\geq 1\%$)
Intervention	<p>Test Immunohistochemistry testing for PD-L1 to determine if the proposed PBS requirements relating to access to pembrolizumab are fulfilled</p> <p>Drug Pembrolizumab</p> <p>Co-dependence Access to pembrolizumab in patients who fulfil the PBS requirements with regards to PD-L1 expression status determined by PD-L1 IHC testing.</p>
Comparator	<p>Test No PD-L1 testing. A supplementary comparison will be presented between the evidentiary standard (Market Ready Assay) and any alternative PD-L1 tests for which there is data in the public domain.</p> <p>Drug Main comparator: Carboplatin/cisplatin+gemcitabine, followed by pemetrexed maintenance in appropriate patients</p> <p>Co-dependence No PD-L1 testing and management with carboplatin/cisplatin+gemcitabine, followed by pemetrexed maintenance in appropriate patients No PD-L1 testing and management with pembrolizumab</p>
Outcomes	<p>Test Outcome measures suitable to assess the analytic performance of PD-L1 IHC testing include:</p> <ul style="list-style-type: none"> • Sensitivity • Specificity • Positive Predictive Value • Negative Predictive Value • Receiver Operating Characteristic (ROC) <p>Measures of comparative performance of PD-L1 testing methods:</p> <ul style="list-style-type: none"> • Concordance with other commercially available PD-L1 antibodies • Comparison with other assays for determining response to anti-PD-L1 treatment • Rates of re-testing <p>Measures of clinical utility</p> <ul style="list-style-type: none"> • Outcomes with pembrolizumab treatment with and without PD-L1 testing <p>Other considerations</p> <ul style="list-style-type: none"> • Rates of re-biopsy • Anticipated test turnaround time. • The estimated number of patients being tested • The number of patients tested per case of PD-L1 positive ($\geq 50\%$ and $\geq 1\%$) result detected • The number of patients tested per case of PD-L1 positive ($\geq 50\%$ and

PICO	Comments
	<p>≥1%) result treated with pembrolizumab</p> <ul style="list-style-type: none"> • The cost of testing per case of PD-L1 positive(≥50% and ≥1%) NSCLC detected • The cost of testing per case of PD-L1 positive (≥50% and ≥1%) NSCLC treated with pembrolizumab. <p>Drug Outcomes Measures of clinical efficacy for pembrolizumab include: Primary outcome:</p> <ul style="list-style-type: none"> • Overall survival • Progression free survival <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Objective tumour response rates (complete response or partial response according to RECIST and irRC criteria) • Quality of life • Disease control rate (response rate + rate of stable disease) • Duration of response • Rate of disease progression • Time to progression • Safety and tolerability.

Table 9 For investigative services

Prior tests	Initial biopsy and tests to confirm diagnosis of NSCLC and EGFR/ALK testing if nonsquamous or NOS.
Reference standard	The evidentiary standard is the Market Ready Assay

Healthcare resources

Healthcare resources that are most likely to be affected, should PD-L1 testing and treatment with pembrolizumab become available include (see table 10):

- Cost of the PD-L1 antibody and pathologists time in interpreting and reporting the results. Pathology laboratories are likely to have all the required equipment for IHC as it is routinely performed.
- Costs of a second biopsy if there is insufficient tissue for PD-L1 testing
- Costs of treating PD-L1 positive patients with pembrolizumab
- Cost offsets from reduced use of displaced treatments.
- Costs for treating adverse events from treatment (with any therapeutic agent).
- Costs associated with ongoing patient monitoring, e.g. physician visits.
- Health care resources associated with initial diagnosis are assumed to remain unchanged and may be excluded from the analysis accordingly.

Questions for public funding

Primary question for public funding

What is the safety, effectiveness, and cost-effectiveness of PD-L1 testing to determine eligibility for pembrolizumab treatment in NSCLC patients whose tumours are EGFR wild type and ALK translocation negative and express PD-L1 ($\geq 50\%$)

FINAL

Table 10 List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
Equivalent to current practice			To be provided in submission	To be provided in submission						
Resources provided to deliver proposed intervention (PD-L1 IHC test and pembrolizumab)										
PD-L1 IHC testing	MBS	Pathology lab	To be provided in submission	To be provided in submission						
Additional biopsy (if required)	MBS	Public or private hospital	To be provided in submission	To be provided in submission						
Resources provided in association with proposed intervention										
Pembrolizumab for patients deemed eligible based on PBS criteria	PBS	Outpatient	To be provided in submission	To be provided in submission						
Administration cost for pembrolizumab	Hospitals/MBS	Inpatient/outpatient and public and private hospitals	To be provided in submission	To be provided in submission						
Physician visits (Oncologist or respiratory physician)	MBS	Outpatient	To be provided in submission	To be provided in submission						
Clinical monitoring (radiological or other imaging, blood counts)	MBS	Outpatient	To be provided in submission	To be provided in submission						
Treatment of adverse events	PBS	Outpatient	To be provided in submission	To be provided in submission						

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided in association with comparator 1 (no testing followed by docetaxel) (e.g., pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)										
Pharmaceuticals (relevant pre-medications, carboplatin/cisplatin+gemcitabine) followed by pemetrexed maintenance if appropriate	PBS	Outpatient	To be provided in submission	To be provided in submission						
Administration cost for carboplatin/cisplatin+gemcitabine followed by pemetrexed maintenance if appropriate	Hospitals/MBS	Inpatient/outpatient and public and private hospitals	To be provided in submission	To be provided in submission						
Physician visits (Oncologist or respiratory physician)	MBS	Outpatient	To be provided in submission	To be provided in submission						
Clinical monitoring (radiological or other imaging, blood counts)	MBS	Outpatient	To be provided in submission	To be provided in submission						
Treatment of adverse events	PBS	Outpatient	To be provided in submission	To be provided in submission						

* Include costs relating to both the standard and extended safety net.

References

Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non–small-cell lung cancer. *N Engl J Med*. DOI: 10.1056/NEJMoa1501824

Gandhi et al, 2014, MK-3475 (anti-PD-1 Monoclonal antibody for non-small cell lung cancer (NSCLC): Antitumour activity and association with tumor PD-L1 expression, *Cancer Res* 2014;74: CT105. Abstract

Herbst et al, 2015, Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial, DOI: [http://dx.doi.org/10.1016/S0140-6736\(15\)01281-7](http://dx.doi.org/10.1016/S0140-6736(15)01281-7)

PRELIMINARY