



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 1414

October 2015

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, should MSD decide to lodge an integrated co-dependent submission for use of the PD-L1 test to determine eligibility for pembrolizumab.

To provide context for the remainder of this application, the next two sections will outline the proposed role of the PD-1 pathway in NSCLC and clinical trial data highlighting a potential predictive role of PD-L1 expression in determining response to pembrolizumab in NSCLC.

A full of overview of these results are outlined in Garon et al 2015. The role of PD-L1 as a predictive biomarker is summarised in Patel et al, 2015.

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.

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]

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 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, EGFR 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

The patient population which would benefit from PD-L1 testing are locally advanced or metastatic (stage IIIb/IV) NSCLC patients (squamous, non squamous and not otherwise specified). Depending on the approved clinical placement of the test, these patients may be newly diagnosed and may not have received any treatment. Alternatively, they may also have failed platinum-based therapy and EGFR or ALK targeted therapy, if applicable. The outcome of this test will determine whether the patients are eligible for subsequent treatment with pembrolizumab.

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.

Evidence for the proposed population

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 **Error! Reference source not found..**

Table 1: 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 measurable 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)

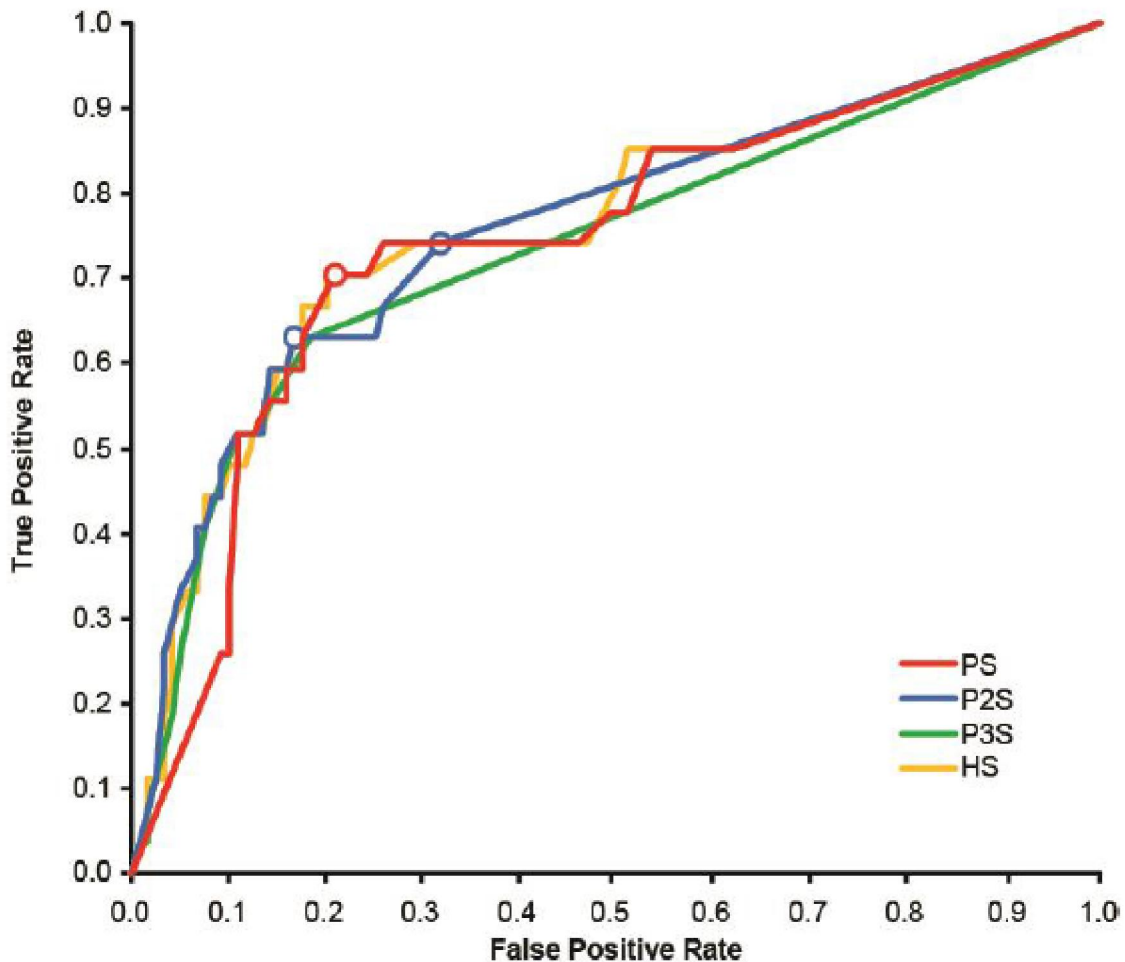
Receiver operating characteristic (ROC) analysis was employed to develop a PD-L1 expression scoring system and to define potential PD-L1 cut points which were associated with an enhanced response to pembrolizumab.

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). The clinical utility of PD-L1 expression in predicting response to treatment with pembrolizumab is being tested more rigorously in the Keynote 010 trial.

Keynote 010

Keynote 010 is a prospective randomised-controlled trial designed to assess the efficacy and safety of pembrolizumab treatment compared to docetaxel in PD-L1 positive NSCLC patients who have failed platinum-based chemotherapy.

Data from KN010 will represent the pivotal evidence presented in MSD's co-dependent submission to support listing of pembrolizumab as a 2nd/3rd line therapy in patients with NSCLC.

Key inclusion criteria of the KN010 trial are that patients must have been determined to be expressing PD-L1 and that they have failed platinum-based therapy (and an EGFR TKI or crizotinib, if eligible).

Key characteristics of the KN010 trial are outlined in **Error! Reference source not found.**

Table 2: Trial design for Keynote 010

Trial	Patient population	Study design	Sample Size and Endpoints
Keynote 010	<ul style="list-style-type: none"> • PD-L1 positive NSCLC • Progressive disease following platinum doublet and EGFR / ALK targeted therapy, if applicable 	Multi-center, worldwide, adaptively designed Phase II/III Randomized (1:1:1) <ul style="list-style-type: none"> • 2mg/kg Q3W Pembrolizumab • 10 mg/kg Q3W Pembrolizumab • Docetaxel 75 mg/m² Q3W 	N=estimated at 920 Primary endpoints <ul style="list-style-type: none"> • Overall Survival REDACTED • REDACTED • Progression free survival REDACTED • REDACTED • Safety • Discontinuations

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.

Given its role in screening tumour samples through the biomarker cutpoint determination of the KN001 trial, as well as screening patients to determine their eligibility for enrolment in KN010, MSD nominates the Clinical Trial Assay (CTA) as the evidentiary standard for PD-L1 expression testing associated with pembrolizumab treatment.

A detailed comparison of the kit components for Clinical Trial Assay and Market Ready Assay will be presented for MSAC's consideration in the co-dependent technology submission. Results of comparative test performance studies between the Clinical Trial Assay and Market Ready Assay will also be presented.

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.

Category 6 – Pathology Services
MBS item number

Immunohistochemical examination of biopsy material by immunoperoxidase or other labelled antibody techniques using the 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

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 Health⁴.

Table 3: Incidence of NSCLC

No. of patients including all lung cancers (2014)	11,580 ¹
Incidence of all NSCLC	66% (based on 2002-2007) ²
No. of lung cancer deaths (2014)(proxy for no. of patients with locally advanced/metastatic disease)	8,630 ³
Estimate of No. pts of locally advanced/metastatic NSCLC	66% * 8630 = 5,696
Eligible patient pool for PD-L1 testing	5,696

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

³Cancer in Australia: an overview 2014, AIHW, Table 7.2, Pg 49 of document, [Cancer in Australia an overview 2014, AIHW](#)

⁴1250-ALK-Final DAP-Accessible, Pg 8 of document

Reference standard

Currently there are no commercially available diagnostic kits for PD-L1 testing. Thus, PD-L1 testing is not currently being carried out on NSCLC patients in Australia, apart from testing in the clinical trial or research setting.

As PD-L1 testing is not part of the current treatment algorithm for NSCLC patients, there is no reference standard for PD-L1 testing on the Medical Benefits Scheme. In place of a reference standard, it is proposed that the co-dependent technology submission nominates PD-L1 testing using the Clinical Trial Assay used to screen for eligibility to KN010 as the “evidentiary standard”. A comparison of assay characteristics and performance between the Market Ready PD-L1 assay and the Clinical Trial assay (evidentiary standard) will be provided and presented for review by MSAC.

Delivery of proposed medical test

Where service would be delivered

As IHC is a common procedure 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. Whilst many patients for whom PD-L1 testing is done would be outpatients (MBS pays testing costs), some patients may also be inpatients (state government pays testing costs).

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

As per the protocol for Keynote 010, 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 is 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. It has not yet been submitted to the PBAC for the treatment of advanced NSCLC, but will be in the near future.

In line with the clinical trial data from KN010, the proposed re-imburement for pembrolizumab is for locally advanced or metastatic (Stage IIIb/IV) NSCLC PD-L1 positive patients who have failed platinum-based therapy. They may also have previously used a targeted therapy such as erlotinib, gefitinib or crizotinib if eligible.

The definition of PD-L1 positivity associated with access to PBS-listed pembrolizumab will be informed by the PD-L1 expression testing protocol employed in the KN010 trial as well as in consideration of the final trial results.

Comparator

Test

It is proposed that the MSAC submission provides comparisons between the evidentiary standard (Clinical Trial Assay) and the Market Ready Assay. It is further proposed that an assessment of comparative assay performance for any alternate PD-L1 test(s) reported in the public domain be presented for consideration by MSAC. This assessment will also consider alternative cut points used for alternative PD-L1 tests.

Drug

In patients with locally advanced or metastatic NSCLC, after failure of platinum-based therapy (and EGFR or ALK targeted therapy, if applicable), pemetrexed (non squamous) or docetaxel (all histologies) are potential treatment options. However, pemetrexed is frequently used as first line maintenance therapy in non-squamous NSCLC patients without progressive disease, thereby excluding it as a 2nd line therapy option in these patients.

Therefore, in the setting in which pembrolizumab reimbursement is being sought, docetaxel is expected to be the main comparator with pemetrexed representing a secondary comparator in non-squamous NSCLC patients that did not receive pemetrexed as a 1st line therapy.

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 docetaxel/pemetrexed
- No PD-L1 testing and management with pembrolizumab

Clinical claim for the proposed medical service

The hypothesis being tested in the KN010 clinical trial is that PD-L1 testing followed by treatment with pembrolizumab in PD-L1 positive patients 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).

The final clinical claim made in the reimbursement submission will be driven by the results of the KN010.

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:

- Concordance with evidentiary standard (Clinical Trial Assay)
- Rates of re-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 result detected
- The number of patients tested per case of PD-L1 positive result treated with pembrolizumab
- The cost of testing per case of PD-L1 positive NSCLC detected
- The cost of testing per case of PD-L1 positive 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 in two circumstances:

- 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 there would be no increase in re-biopsy rate in this instance.
- If MSAC recommend PD-L1 testing be performed on newly obtained tissue (formalin-fixed paraffin-embedded section within 42 days of biopsy) after failure of platinum-based chemotherapy (See **Clinical Management Algorithm Figure 4**). In this situation all patients who have failed platinum-based chemotherapy (and thus would be eligible for pembrolizumab) would be required to undergo an additional biopsy to source fresh tissue for PD-L1 testing. In this scenario these re-biopsies would be additional to the current standard of care.

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)

Type of economic evaluation

The decision regarding the structure of the economic evaluation will be made in consideration of the data reported in the KN010 clinical trial, and the determination of which patient sub group(s) are reported as deriving the most clinical benefit from treatment with pembrolizumab.

In the context of the KN010 being designed as a superiority trial, it is anticipated that a cost-utility evaluation will be presented.

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 report the results.

Clinical Management Algorithm - clinical place for the proposed intervention

Current treatment algorithm

The current treatment algorithm is outlined in Figure 2. For the purposes of this algorithm, the sponsor has assumed that :

1. Afatinib is PBS listed for patients with EGFR mutations.
2. After histological confirmation of NSCLC, biomarker tests are conducted (for EGFR and ALK) on non squamous and NOS (Not otherwise specified) patients to 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). These patients will then receive a platinum doublet (e.g. cisplatin/gemcitabine) on progression. All other patients (non squamous patients who are EGFR wildtype or ALK translocation negative and those with squamous histology) will be treated with a platinum doublet (e.g. cisplatin and gemcitabine) as the initial therapy. Pemetrexed is used as a first line maintenance therapy for some non squamous patients without progressive disease.
3. When patients progress following platinum doublet therapy (without or without pemetrexed maintenance), the majority are treated with docetaxel; pemetrexed is also used, but to a lesser extent, due to its use as maintenance therapy in the first line setting in some non squamous patients.

Future treatment algorithms

The optimal placement of PD-L1 testing in the treatment algorithm for NSCLC is to be determined. Aspects of PD-L1 testing which will inform the appropriate placement of testing in the clinical algorithm are:

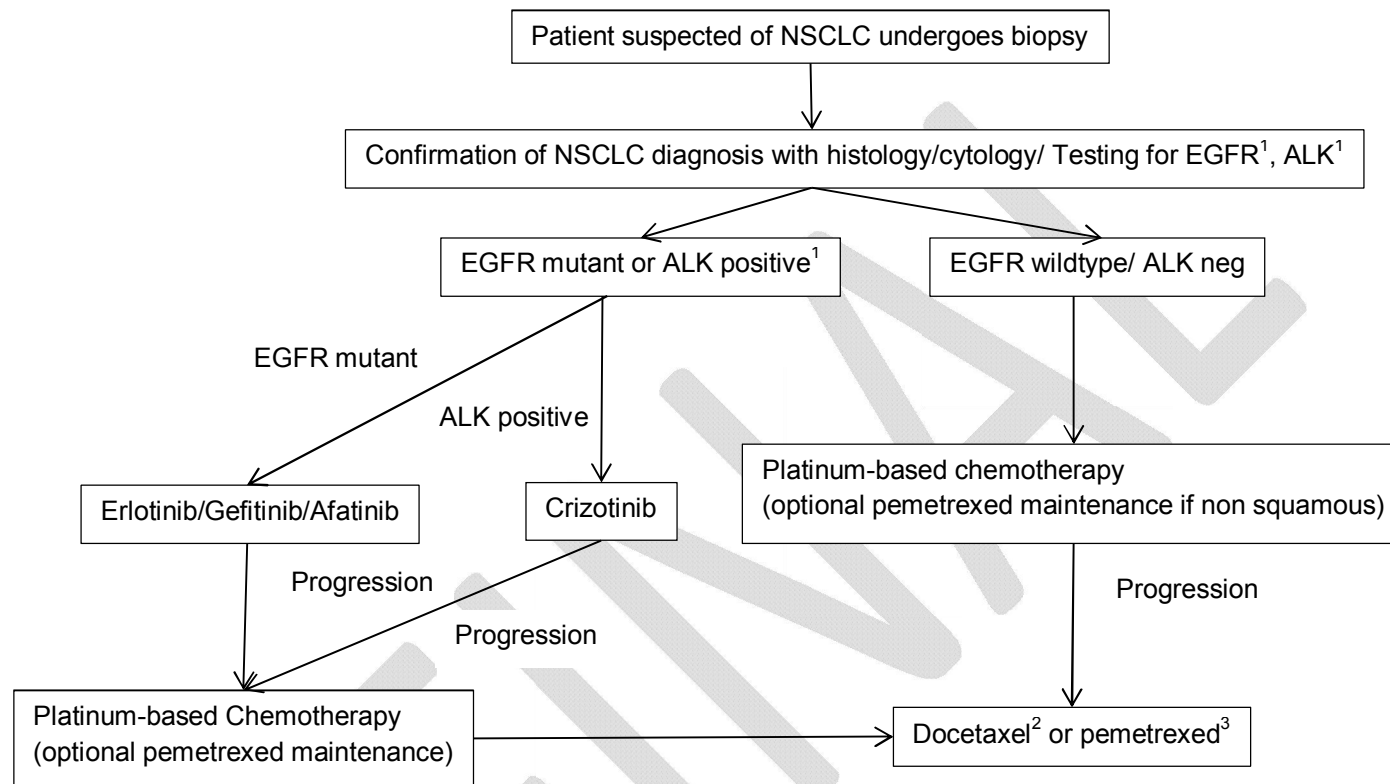
- Whether PD-L1 expression is altered by stage of disease or prior chemotherapy
- Whether the PD-L1 antigen is stable over time

MSD commits to reviewing the evidence regarding changes in PD-L1 expression as part of the co-dependent technology submission to inform the optimal place in therapy of the test

The sponsor proposes that there are three possible scenarios regarding the timing of the PD-L1 test.

- **Testing on recently cut (within 6 months) sections from initial biopsy, performed at the time of other biomarker assessment. (Figure 3)** PD-L1 IHC to be done with ALK IHC and other diagnostic IHC tests and in parallel to EGFR testing. 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.
- **Testing on recently cut (within 6 months) sections from archived initial biopsy, performed at the time of progression after failed platinum-based therapy (Error! Reference source not found.)** PD-L1 IHC testing to be done prior to 2L+ treatment on tissue obtained from first biopsy whilst EGFR and ALK IHC testing done prior to 1st line treatment on tissue obtained from first biopsy.
- **Testing performed on a newly obtained (contemporaneous) biopsy obtained not more than 42 days before testing, after failure of platinum based therapy (Error! Reference source not found.)** PD-L1 IHC testing to be done prior to 2L+ treatment on tissue obtained from a second biopsy, whilst EGFR and ALK IHC testing would be done prior to 1st line treatment on tissue obtained from first biopsy. This scenario requires a second biopsy which has exposes patients to risks such as pneumothorax (See **Risks to patient**). There may also be a significant number of patients who are not healthy enough for the second biopsy. In terms of the consequences of PD-L1 testing, patients who test positive will be eligible for pembrolizumab instead of docetaxel/pemetrexed (in red font) The appropriate definition of PD-L1 positive in the context of determining eligibility to pembrolizumab will be determined through the co-dependent technology submission process

Figure 2: Current treatment algorithm



¹ non squamous or NOS histologies only
² Squamous or prior pemetrexed maintenance
³ Non squamous if no prior maintenance therapy

Figure 3: Treatment algorithm showing PD-L1 testing after histological diagnosis using newly obtained tissue⁶ from 1st biopsy and subsequent pembrolizumab treatment

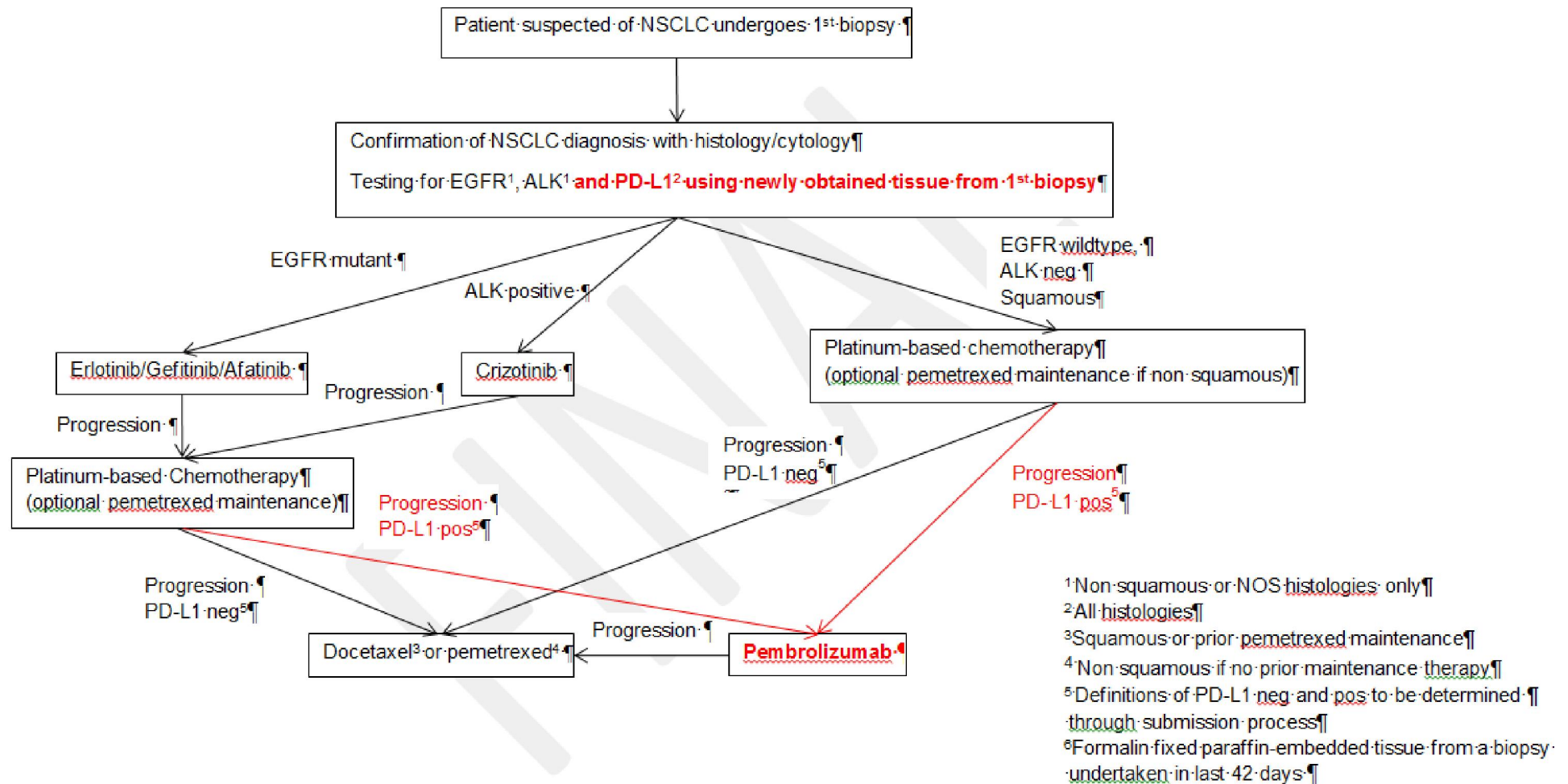


Figure 4: Treatment algorithm showing PD-L1 testing after failure of platinum-based therapy using archived tissue from 1st biopsy and subsequent pembrolizumab treatment

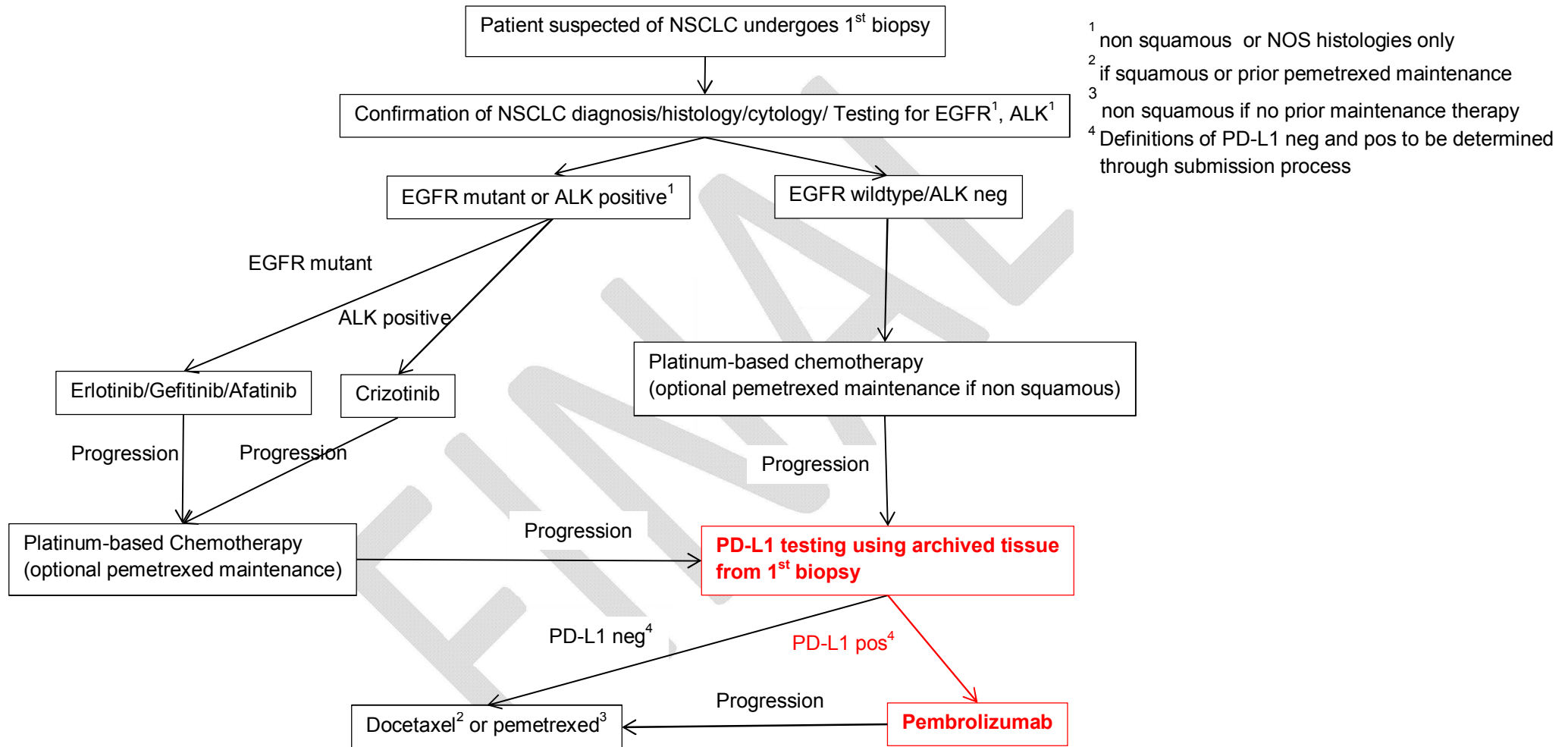
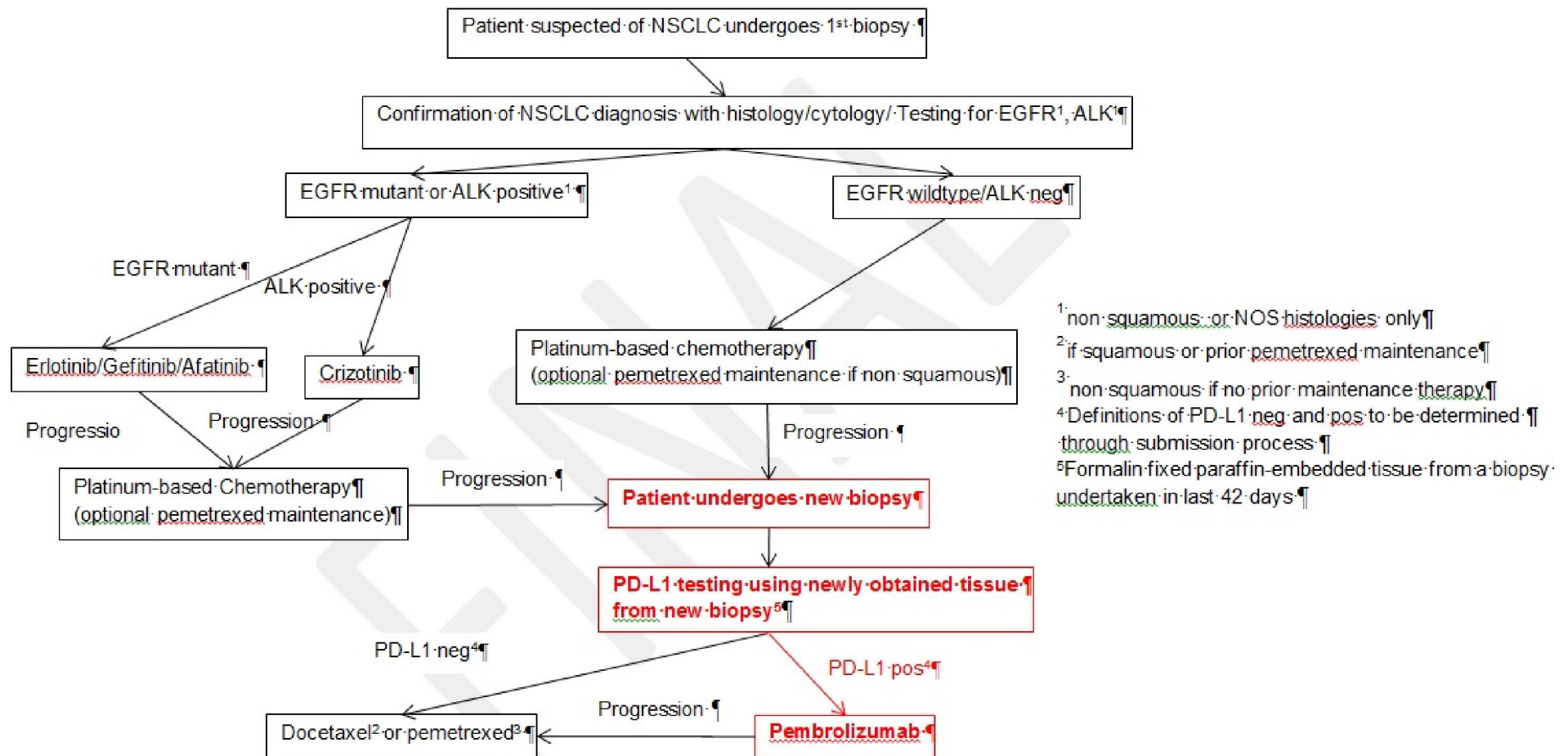


Figure 5: Treatment algorithm showing PD-L1 testing after failure of platinum-based therapy using newly obtained tissue from new biopsy and pembrolizumab treatment



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 the co-dependent technology submission.

Pembrolizumab is currently TGA-approved as a treatment for melanoma regardless of PD-L1 status (ARTG ID: 226597). MSD anticipates filing for an expanded TGA indication to include patients with NSCLC under the parallel TGA and PBAC assessment process.

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 4,

Table 5 and Table 7

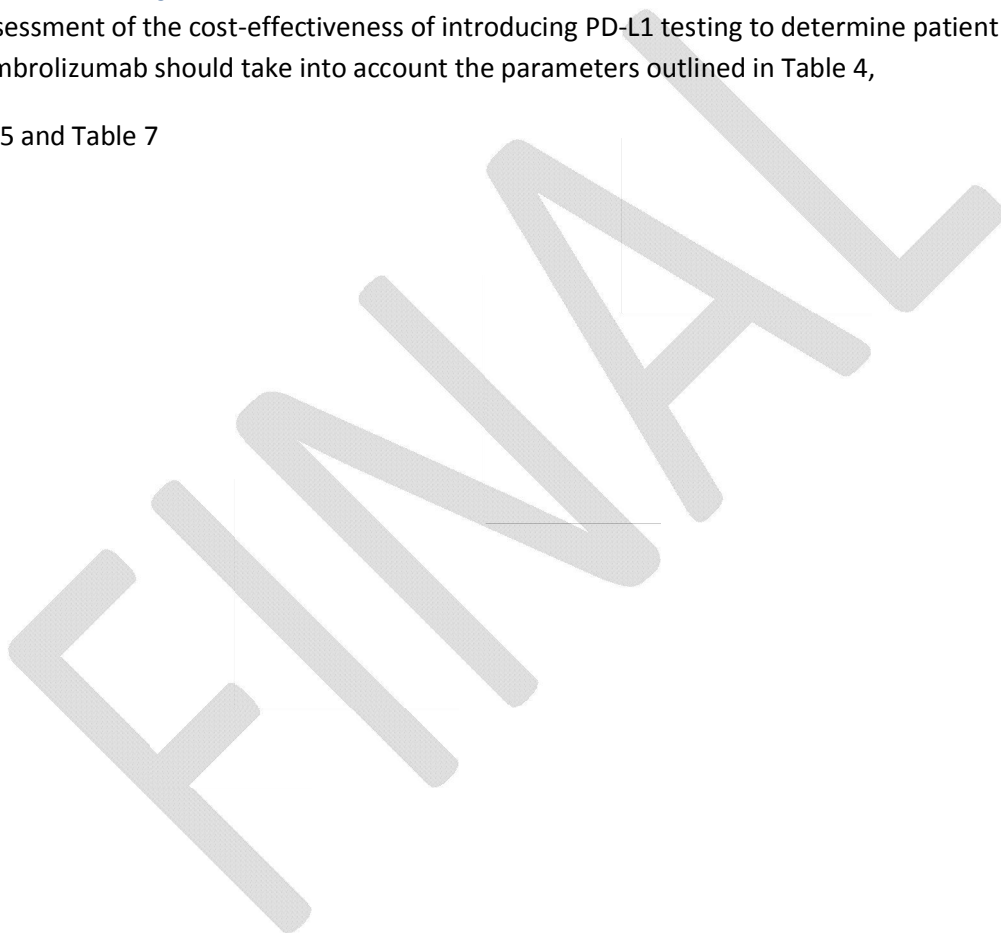


Table 4: Summary of PICO to define research question

PICO	Comments
Patients	Patients with locally advanced or metastatic non-small cell lung cancer (squamous and non squamous)
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 treatment for PD-L1 positive patients</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. Comparisons will also be made between the evidentiary standard (Clinical Trial Assay) and any alternative PD-L1 test (such as the Market Ready Assay) for which there is data in the public domain or available to the sponsor</p> <p>Drug Main comparator: Docetaxel Secondary comparator: Pemetrexed</p> <p>Co-dependence No PD-L1 testing and management with docetaxel/pemetrexed. 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 evidentiary standard (Clinical Trial Assay) • Rates of re-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 result detected • The number of patients tested per case of PD-L1 positive result treated with pembrolizumab • The cost of testing per case of PD-L1 positive NSCLC detected • The cost of testing per case of PD-L1 positive 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>

PICO	Comments
	<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 5: For investigative services

Prior tests	Initial biopsy and tests to confirm diagnosis of NSCLC. Depending on the final clinical algorithm chosen, PD-L1 testing may use: <ul style="list-style-type: none"> • newly obtained or archived tissue from initial biopsy • newly obtained tissue from a new biopsy performed after failure of platinum-based therapy
Reference standard	There is no reference standard. The Clinical trial assay used to determine patient eligibility in KN010 is the evidentiary standard

Healthcare resources

Healthcare resources that are most likely to be affected, should PD-L1 testing and treatment with pembrolizumab become available include (see Table 7):

- 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 or it is deemed that PD-L1 testing should be done on newly obtained tissue after failure of platinum-based treatment.
- Costs of retrieving tissue blocks if PD-L1 testing is undertaken on archival tissue. 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 and 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 patients with locally advanced or metastatic NSCLC who have failed platinum-based chemotherapy compared with current practice (no PD-L1 testing and docetaxel treatment after failure of platinum-based chemotherapy)?

This question could be evaluated in three scenarios as outlined in Table 6

Table 6: Potential cost effectiveness scenarios to be investigated

When to test	Eligible PD-L1 positive population
PD-L1 test performed at the time of other biomarker tests using newly obtained tissue from 1 st biopsy	Scenario 1
PD-L1 test performed after failure of platinum-based chemotherapy on archived tissue from 1 st biopsy	Scenario 2
PD-L1 test performed after failure of platinum-based chemotherapy on newly obtained tissue from a new biopsy	Scenario 3

FINAL

Table 7: 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 lung biopsy (depending on place in therapy of test)	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	Blend of 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, docetaxel/pemetrexed)	PBS	Outpatient	To be provided in submission	To be provided in submission						
Administration cost for docetaxel/pemetrexed	Hospitals/MBS	Blend of 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.

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