Australian Government

Department of Health

RATIFIED PICO

Application 1522:

Programmed cell death-ligand 1 (PD-L1) immunohistochemistry testing for access to pembrolizumab (monotherapy or combination therapy) as first-line therapy for patients with recurrent (not amenable to local treatment) or metastatic head and neck squamous cell carcinoma (HNSCC) - (Codependent application)

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	**Test:** Patients with either recurrent head and neck squamous cell carcinoma (HNSCC) that is not amenable to local treatment, or metastatic HNSCC. **Drug:** Patients who are Programmed Death Ligand 1 (PD-L1) positive (defined as a combined positive score (CPS; tumour cells, lymphocytes and macrophages) of ≥1 will be eligible for pembrolizumab (monotherapy or in combination with chemotherapy (platinum + 5-fluorouracil [5-FU])).
Prior tests	Routine histology, cytology and immunohistochemistry tests to confirm diagnosis of recurrent or metastatic HNSCC.
Intervention	**Test:** The programmed cell death ligand-1 (PD-L1) test involves taking a biopsy of the tumour and performing an immunohistochemical assay to detect the level of PD-L1 expression within a tumour. **Drug:** First-line treatment with pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy (platinum + 5-fluorouracil [5-FU]), in those with PD-L1 expression measured as a CPS of ≥1.
Comparator	No PD-L1 test and the subsequent continuation of standard of care.
Outcomes	**Safety outcomes:** Adverse events relating to tolerability and toxicity of pembrolizumab treatment. **Test-related:** Efficacy and safety outcomes of pembrolizumab and treatment with and without prior PD-L1 testing; re-biopsy rates. **Treatment-related:** Overall survival; disease-specific survival; progression-free survival; time to progression; rate of recurrence; time to recurrence; overall response rate; duration of response; quality of life. **Test outcomes:** Trial-based PD-L1 IHC assay analytical performance; comparative performance of PD-L1 testing methods; re-testing rates. **Cost-effectiveness:** Cost per life year gained; cost per QALY gained. **Healthcare resources:** Cost of testing per case of CPS <1; re-biopsy rates; test turn-around time; estimated number of patients tested. **Net Australian Government healthcare costs:** Net cost to the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS).

PICO rationale

BACKGROUND

This PICO was considered by PASC on two separate occasions. The first consideration took place in April 2018 and the application was put on hold, pending the availability of clinical trial results. The second consideration took place in April 2020. PASC's updated advice, as provided in April 2020 and related applicant comments have been included within the document using *italics*.

POPULATION

The patient population for whom public funding of the proposed medical service is intended includes patients with head and neck squamous cell carcinoma (HNSCC) that is (i) recurrent (not amenable to local treatment, who have resectable or unresectable disease) or (ii) metastatic. The applicant proposed that access to first-line treatment with pembrolizumab be based on a minimum PD-L1 expression.

The application stated that head and neck cancer includes cancers from 18 different sites including those that occur in the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid and salivary glands and is the fifth most common cancer worldwide, accounting for 5% of all malignancies. In Australia, head and neck cancer was the seventh most commonly diagnosed cancer in Australia in 2013, with 4,409 new cases. In 2014, head and neck cancer was the fifteenth leading cause of cancer death in Australia. More recent data reports that head and neck cancers are ranked fifth in males (3,625 estimated cases in 2017), eleventh in females (1,330 estimated cases in 2017), and eighth overall (4,955 estimated cases in 2017) (AIHW 2017). Most head and neck cancers arise from squamous cells (Sanderson & Ironside 2002).

HNSCC is closely associated with cigarette smoking, alcohol consumption and poor oral health in patients in Western countries (Sanderson & Ironside 2002). Recently, human papilloma virus (HPV) has been implicated in an increasing number of cases of HNSCC (Economopoulou et al 2016). The application also stated that Epstein-Barr virus and cytomegalovirus have also been associated with an increased incidence of head and neck cancers.

Symptoms of head and neck cancers may include a lump or a sore that does not heal, a persistent sore throat, difficulty swallowing, and a change or hoarseness in the voice (NIH Fact Sheet). Other site specific symptoms may include a white or red patch on the gums, the tongue, or the lining of the mouth; a swelling of the jaw; difficulty speaking or breathing; difficulty hearing, headaches; and ear pain (NIH Fact Sheet).

A large number of patients with HNSCC present with locally advanced-stage disease (Stage III-IV) with a significant proportion developing disease recurrence after site-specific multimodality therapy (Sacco & Cohen 2015). Survival rates for patients with tumour recurrence or metastatic disease are poor (Economopoulou et al 2016), with survival rates falling as tumours grow and metastasise (Sanderson & Ironside 2002; Tinhofer et al 2016).

Initial treatment usually involves a combination of chemotherapy, radiotherapy and/or surgery, and this can result in disease control for an estimated 33-86% of patients. Patients who progress following this initial treatment have recurrent disease and require subsequent treatment. In patients who present with metastatic disease, therapy is usually the same as for patients who develop recurrent disease following initial treatment.

PD-L1 testing is proposed as a means of determining which patients would be eligible for receiving the codependent drug, pembrolizumab, as monotherapy or as combination therapy. The applicant proposed that programmed cell death-ligand 1 (PD-L1) testing would be utilised to determine eligibility for pembrolizumab therapy as first-line treatment. The KEYNOTE-048 trial provides evidence of the use of pembrolizumab as monotherapy or in combination with a platinum-based drug and 5-flurouracil [5-FU] use as first-line treatment in patients with recurrent or metastatic HNSCC. The trial indicated that PD-L1 expression measured as a CPS of ≥1 is a marker for improved efficacy with pembrolizumab monotherapy.

The applicant advised that pembrolizumab is currently TGA-registered for second-line treatment of patients with recurrent or metastatic HNSCC, with disease progression on or after platinum-containing chemotherapy. TGA registration was based on the open-label KEYNOTE-055 study, with no designation for a biomarker.

PASC previously noted a number of codependent applications have been submitted for MBS funding of PD-1/PD-L1 testing: in non-small cell lung cancer (NSCLC); head and neck squamous cell carcinoma (HNSCC); urothelial cancer; and triple negative breast cancer (TNBC) (Table 1). Applications 1414 and 1440 (later-line and first-line NSCLC, respectively) were not supported by MSAC. The latter was successfully re-submitted as Application 1440.1, and a PD-L1 test in patients with NSCLC is now included on the MBS (Item 72814). The other applications detailed in Table 1 have not yet been considered by MSAC, except for MSAC 1570, which was considered at the April 2020 MSAC meeting.

Table 1: Previous and current MSAC applications for PD-1/PD-L1 testing

Application	Patient group	PD-1/PD-L1 threshold	Codependent medicine	Applicant
1414, 1440, 1440.1 – MBS item 72814 listed on 1 January 2019	NSCLC	TPS ≥50%	Pembrolizumab	MSD
1445	Bladder cancer	CPS ≥1%	Pembrolizumab	MSD
1453	Mesothelioma	TPS ≥1%	Pembrolizumab	MSD
1457	Urothelial	Not reported	Pembrolizumab	MSD
1505	HNSCC	TPS ≥25% (mono) TPS <25% (combo)	Durvalumab or durvalumab/ tremelimumab combination therapy	--
1506 (Application withdrawn)	Urothelial	TC ≥25% +ve; or if >1% IC, ≥25% +ve; or if ≤1% IC, 100% +ve	Durvalumab or durvalumab/ tremelimumab combination therapy	--
1570	TNBC	≥1% IC	Atezolizumab	--

Source: relevant Public Summary Documents, PICO Confirmations or Application Forms from http://www.msac.gov.au
AZ = AstraZeneca; CPS = combine positive score (tumour + inflammatory cells); HNSCC = head and neck squamous cell carcinoma; IC = immune cells; MSD = Merck, Sharp & Dohme; NSCLC = non-small cell lung cancer; TNBC = triple negative breast cancer; TPS = tumour proportion score (tumour cells)

Rationale

The population is patients with metastatic or recurrent HNSCC as described above. *PASC confirmed that all patients with a diagnosis of recurrent head and neck squamous cell carcinoma (HNSCC) who are not amenable to local treatment, or metastatic HNSCC, would be eligible for PD-L1 testing to inform the treatment decision for pembrolizumab monotherapy or combination therapy.*

The results for overall survival in KEYNOTE-048 are presented in Figure 1 and Table 2 below. *Since the April 2020 consideration, the applicant has advised that the threshold for PD-L1 expression for eligibility for pembrolizumab monotherapy or combination therapy will be a combined positive score (CPS) of 1 or more (≥1). Therefore, the applicant is requesting CPS ≥1 for both the pembrolizumab monotherapy and pembrolizumab + chemotherapy populations for the codependent submission, as these populations are supported by the clinical evidence.*

The CPS measures the number of PD-L1 stained cells, including tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells, multiplied by 100. Despite its derivation, the CPS is expressed as a value and not a percentage, and although the result can exceed 100, the maximum score is defined as CPS 100. The KEYNOTE-048 trial also tested the thresholds of a CPS or 20 or more (≥20), ≥1, as well as efficacy in the total population (regardless of PD-L1 status).

The examined thresholds of CPS ≥20 or ≥1 were defined, based on evolving information obtained from further analysis of the KEYNOTE-012 and KEYNOTE-055 studies. KEYNOTE-012 enrolled participants with advanced triple negative breast cancer, advanced head and neck cancer, advanced urothelial cancer, or advanced gastric cancer; KEYNOTE-055 enrolled patients with recurrent or metastatic HNSCC after treatment with platinum-based and cetuximab therapy.

Information provided by the applicant indicated that preliminary biomarker results from KEYNOTE-012 showed that, when tumour and inflammatory cells were used to score PD-L1 status, an increase in overall response rate (ORR) was observed between PD-L1 positive (PD-L1+) versus PD-L1 negative (PD-L1-) tumours (P=0.023). However, this increase was not observed when scoring was restricted to tumour cells only (or tumour proportion score; TPS).

Improved progression-free survival (PFS; P=0.026) and overall survival (OS; P=0.008) were also observed in PD-L1+ versus PD-L1- tumours when scoring was conducted by CPS, but not TPS. The applicant contended that, inclusion of both tumour cells and inflammatory cells (CPS) in immunohistochemistry (IHC) scoring, improves the ability to enrich for response, based on PD-L1 status, compared to tumour cells alone (TPS) in subjects with recurrent or metastatic HNSCC. In addition, preliminary results from KEYNOTE-055 showed that using CPS ≥1 and ≥20 thresholds demonstrated a positive predictive value (PPV) of 20.3% and 26.8%, respectively, with negative predictive value (NPV) at 88.0% and 88.3%, respectively. The prevalence for CPS ≥1 and ≥20 cut-points are approximately 80% and 50%, respectively.

The applicant stated that PD-L1 expression was to be evaluated using a prespecified CPS threshold of ≥20 in the KEYNOTE-048 trial, and that the prespecified CPS threshold of ≥1 would also be evaluated. The trial employed a multiplicity strategy to its statistical analyses and nominated a non-inferiority margin for overall survival for the hazard ratio [HR] of 1.2 (Burtness et al 2019).

Results from the KEYNOTE-048 trial demonstrated pembrolizumab monotherapy was non-inferior to cetuximab plus chemotherapy in the total population and that pembrolizumab plus chemotherapy was superior to cetuximab plus chemotherapy in the total population, see Table 2. It is not clear that PD-L1 testing should be required at all given these results; however, restricting pembrolizumab (monotherapy or combination therapy) to those with a CPS ≥1 is consistent with the TGA indication.

Results of the KEYNOTE-048 trial also reported improved OS for pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy, versus cetuximab with chemotherapy, in the CPS ≥20 subgroup and CPS ≥1 subgroup, see Table 2.

PASC noted that in the application, patients who are PD-L1 positive (combined positive score [CPS] ≥1) would be eligible for pembrolizumab monotherapy, but that there was no PD-L1 expression threshold for access to pembrolizumab in combination with chemotherapy. However, PASC noted the applicant's advice that regulatory advice was expected soon from the TGA. The applicant foreshadowed that pembrolizumab might be restricted to patients with CPS ≥1 for both monotherapy and combination therapy. PASC considered that this would have implications for the population, MBS item descriptor and clinical management algorithms of the PICO Confirmation discussed during the meeting. PASC also noted the applicant's advice indicating that the selection of pembrolizumab therapy type is based on a patient's other baseline characteristics as well as their PD-L1 status.

PASC noted in the pivotal trial (KEYNOTE-048) that patients were enrolled if they had no prior systemic therapy administered in the recurrent or metastatic setting. In addition, patients were also enrolled if such systemic therapy was completed more than 6 months prior to signing consent and it was given as part of multimodal treatment for locally advanced disease.

PASC previously considered that analyses of treatment-effect variation, based on mutually-exclusive subsets of PD-L1 expression, would be useful for MSAC and PBAC consideration. This is because it would allow the impact of increasing levels of expression on the comparative effectiveness of pembrolizumab to be clarified. It will also be important to report results of overall survival in their respective complement groups, and conduct tests for interaction to demonstrate treatment-effect modification, to support restricting use, based on levels of PD-L1 expression.

The applicant indicated that an abstract to be published in April 2020 will report on final overall survival based on different CPS thresholds. Overall survival is the main and most relevant outcome, but data should be presented similarly for progression-free survival (PFS), and for all relevant CPS thresholds.

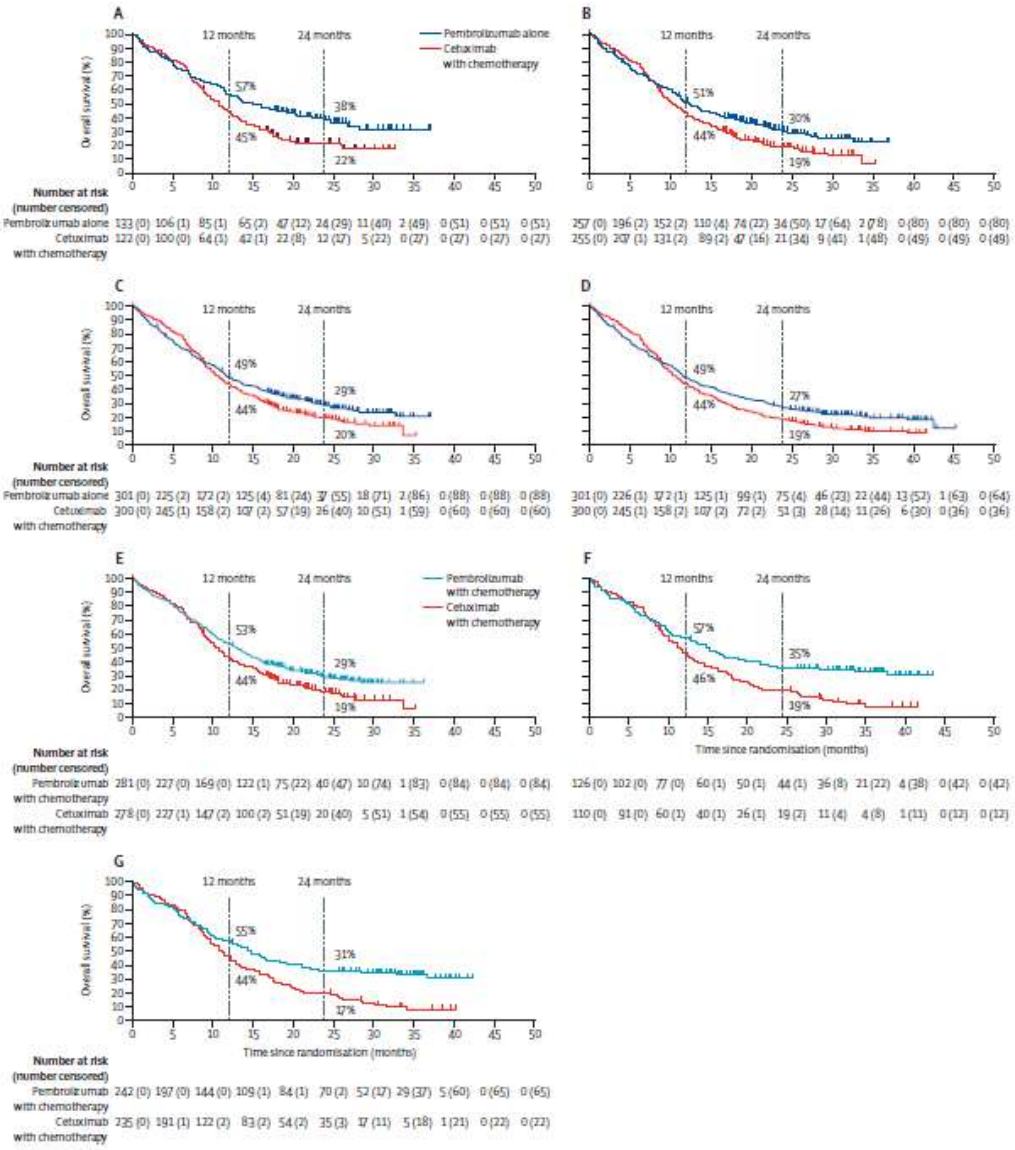

Figure 1: Kaplan-Meier estimates for overall survival

(A) Pembrolizumab monotherapy versus cetuximab + chemotherapy in CPS ≥20 subgroup; second interim analysis
(B) Pembrolizumab monotherapy versus cetuximab + chemotherapy in CPS ≥1 subgroup; second interim analysis
(C) Pembrolizumab monotherapy versus cetuximab + chemotherapy in total population; second interim analysis
(D) Pembrolizumab monotherapy versus cetuximab + chemotherapy in total population; final analysis
(E) Pembrolizumab + chemotherapy versus cetuximab + chemotherapy in total population; second interim analysis
(F) Pembrolizumab + chemotherapy versus cetuximab + chemotherapy in CPS ≥20 subgroup; final analysis
(G) Pembrolizumab + chemotherapy versus cetuximab + chemotherapy in CPS ≥1subgroup; final analysis
Source: Figure 2, p1922 Burtness et al (2019)

Table 2: Results for overall survival reported in KEYNOTE-048

	Treatment (months)	Cetux + chemo (months)	HR (95% CI)	Conclusion (analysis)
Pembrolizumab monotherapy				
Total population	11.6	10.7	0.85 (0.71, 1.03)	Non-inferior, definitive (2nd)
	11.5	10.7	0.83 (0.70, 0.99)	Superiority not met (final)
CPS ≥1 subgroup	12.3	10.3	**0.78 (0.64, 0.96)**	Superior, definitive (2nd)
CPS <1 subgroup	NR	NR	NR	NR
		Test for interaction	NE	
CPS ≥20 subgroup	14.9	10.7	**0.61 (0.45, 0.82)**	Superior, definitive (2nd)
CPS <20 subgroup	NR	NR	NR	NR
		Test for interaction	NE	
Pembrolizumab + chemotherapy				
Total population	13.0	10.7	**0.77 (0.63, 0.93)**	Superior, definitive (2nd)
CPS ≥1 subgroup	13.6	10.4	**0.65 (0.53, 0.80)**	(final)
CPS <1 subgroup	NR	NR	NR	NR
		Test for interaction	NE	
CPS ≥20 subgroup	14.7	11.0	**0.60 (0.45, 0.82)**	(final)
CPS <20 subgroup	NR	NR	NR	NR
		Test for interaction	NE	

Source: Burtness et al (2019)
2nd = second interim analysis; Cetux = cetuximab; Chemo = chemotherapy; CPS = combined positive score; final = final analysis; NE = not estimable; NR = not reported

PASC previously questioned why PD-L1 treatment thresholds and scoring systems in this application (1522) [i.e. CPS versus TPS] differ from those in other codependent applications. *PASC recalled that a previous application for a different codependent medicine had used a different PD-L1 definition (total proportion score [TPS]) and threshold (25%) in the same patient population (Application 1505), and requested that these differences across medicines be justified as they are likely to cause confusion.* The applicant clarified that, due to differences in biology, PD-L1 thresholds/scoring systems vary depending on tumour-type. For example, the PD-L1 threshold for pembrolizumab treatment for HNSCC will be different to that for NSCLC.

The application indicated that pembrolizumab could replace current standard of care in PD-L1 positive recurrent or metastatic HNSCC patients, with an estimated uptake of 100% for PD-L1 testing for all patients diagnosed with recurrent or metastatic HNSCC. The application stated that the risk of leakage for PD-L1 testing is expected to be negligible as testing would be restricted to those patients who are potentially eligible for pembrolizumab as requested.

PD-L1 testing is likely to be undertaken for all patients being considered for pembrolizumab (either as monotherapy or in combination), since knowledge of CPS levels will determine eligibility for pembrolizumab. Treatment choice is likely to depend on how rapidly the patient's disease is progressing and whether the location of the disease is affecting the patient's quality of life. The applicant advised that the majority of patients are expected to be treated with pembrolizumab monotherapy.

Prior test

Prior tests include routine histology, cytology and immunohistochemistry to confirm the diagnosis of recurrent or metastatic HNSCC. Imaging may also be conducted to determine distant metastases or lymph node dissections to understand lymph node involvement.

INTERVENTION

PD-L1 testing

Programmed death ligand-1 (PD-L1) expression by tumour cells and macrophages suppresses immune surveillance and promotes neoplastic growth. The PD-1/PD-L1 axis is co-opted by tumours to evade immune surveillance. Pembrolizumab works to block this axis, resulting in anti-tumour activity.

The application proposed that the PD-L1 test will be required once only per patient. A PD-L1 test involves taking a biopsy of the tumour to detect the percentage of PD-L1 expression within a tumour, by immunohistochemical (IHC) assay. IHC testing is common in Australian pathology laboratories.

The test involves analysing tissue from a biopsy of the tumour to determine the level of PD-L1 expression on the tumour and immune cells. Collection of the biopsy will be predominantly undertaken by a surgeon, with the test itself undertaken by an anatomical pathologist, most likely alongside other histopathology tests. The application stated that information is available on the use of both archival and newly obtained biopsy samples and that this will be presented in the integrated codependent submission. The applicant has advised that in most cases, recently obtained samples are likely to be used.

PASC noted the applicant's advice that the biopsy material for the test should be the most recent sample (which may be archival), and that the main reasons why archival tissue would be used is if the new site of the cancer is difficult to access, or can't be biopsied. PASC confirmed that the biopsy material used for testing should be from the most recent tumour tissue sample available.

The Applicant reiterated that it presented evidence showing concordance of fresh vs archival tissue in the submission, but confirmed that the testing should be done on the most recently obtained sample.

In patients with HNSCC, higher PD-L1 expression is associated with poor prognosis (Lin et al 2015), suggesting that the degree of PD-L1 expression is an important prognostic marker in the management of HNSCC.

PASC confirmed the proposed intervention.

The PD-L1 assay used in studies of pembrolizumab in HNSCC is the PD-L1 IHC 22C3 pharmDx assay. The assay takes between 2.5-4 hours to run depending on the instrumentation and protocol used. This assay was used to assess PD-L1 expression in patients with HNSCC in the KEYNOTE-048 trial. Limited information was presented in the application regarding the test and IHC scoring methodology (CPS), however the applicant has indicated that the methods for obtaining, archiving and staining tissue across the CPS and TPS methods are identical with the reporting differing only in relation to the scoring of immune cells, as these are excluded from the TPS method. The application

stated that detailed information on the assay kit components as well as its performance studies will be presented for MSAC consideration in the integrated codependent submission.

The proposed item descriptor does not restrict PD-L1 testing by assay (i.e. does not specify that the PD-L1 IHC 22C3 pharmDx assay be used to determine eligibility for pembrolizumab). Other PD-L1 IHC assays or alternative tests that predict a response to anti-PD-L1 therapies may be eligible for use. PASC previously queried the interchangeability of alternative assays. Interchangeability of different reagents, such as the antibody, across different platforms should also be considered. The applicant reported pilot results published in an abstract by Vainer et al (2019), which showed greater than 95% concordance between the IHC 22C3 pharmDx assay and the FDA-approved Bench Mark XT assay (with 2/45 discordant scores) based on CPS thresholds of ≥10 and ≥1 in patients with both HNSCC and urothelial carcinoma. The interclass co-efficient was 0.83 for HNSCC. A larger study is ongoing.

PASC previously suggested intra-professional variation should also be considered (i.e. whether one pathologist would score a given test in the same way as another pathologist), acknowledging factors like small biopsy sizes and different scoring systems (for different tumours) add to complexity of interpretation. The applicant suggested that these types of data could be collected in clinical practice as “Real-World Data”.

It was proposed that the test be pathologist-determinable, however the application indicated that specialists, including oncologists, may request PD-L1 testing. The application proposed that a certified pathologist would be responsible for conducting the test and reporting the results, and that 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. PASC previously noted that issues raised in this application remain similar to those raised in other (earlier) codependent PD-L1 applications (i.e. analytical and clinical validity, and clinical utility).

It was proposed that PD-L1 IHC testing be performed in any pathology laboratory holding appropriate accreditation to claim pathology services through the MBS. The application stated that laboratories have the platform infrastructure and reagents to perform PD-L1 IHC testing and that the PD-L1 antibody is the only additional resource required. However, if a specific test (and therefore a specific testing platform) is required, not all laboratories may be able to provide testing without purchase of the specific testing platform unless there is evidence of acceptable concordance of each assay across different platforms.

The application stated that uptake of PD-L1 testing in the proposed population would be high (100%). The justification provided for this was that pembrolizumab therapy (monotherapy or combination therapy) is superior to current standard of care and that patients whose tumours express PD-L1 (defined as a CPS ≥1) will benefit more from pembrolizumab therapy than those whose tumours do not express PD-L1. However, uptake of testing is likely to depend on the comparative effectiveness and safety of pembrolizumab to other therapies in patients who express PD-L1, not whether patients who express PD-L1 benefit more from pembrolizumab treatment than those who do not express PD-L1. On the basis of superiority over standard of care, pembrolizumab is expected to displace platinum- or taxane-based chemotherapies in those who express PD-L1.

The application stated that pathologist training and quality assurance programs would be developed to deliver diagnostic tests for access to treatments targeting the PD-1 pathway on the PBS. Further detail on these would be useful for MSAC consideration.

PASC noted advice from the Royal College of Pathologists of Australasia (RCPA) *in its statement of clinical relevance regarding Application 1522, 'highlighting the importance of Quality Assurance Programs (QAP) and accurate training in the diagnostic evaluation of PD-L1 positivity in this context.' PASC noted the complexity of the test and that the application indicated a quality assurance program (QAP) would need to be developed.*

PD-L1 testing is currently listed on the MBS for patients with NSCLC (MBS Item 72814). The proposed PD-L1 test has been registered with the Therapeutic Goods Administration, including for this indication.

PASC previously noted the Targeted Consultation comment that PD-L1 is an 'imperfect biomarker'.

PD-L1 inhibitor: pembrolizumab

Pembrolizumab is a highly selective humanised monoclonal antibody that targets the PD-1 receptor to potentiate an immune response. PD-L1 expression in HNSCC biopsies can be assessed using IHC testing with antibodies that bind specifically to the PD-L1 protein.

COMPARATOR

The applicant proposed that the appropriate comparator for the purposes of this Application (1522) is no PD-L1 test and the subsequent continuation of standard of care. PASC previously confirmed this was the appropriate comparator. The application indicated that standard of care is considered to be a cytotoxic regimen such as cisplatin or carboplatin together with 5- fluorouracil (5-FU) or a taxane depending on patient characteristics and clinician choice.

Pembrolizumab is proposed to be used in eligible patients whose tumours are found to express PD-L1, defined as a CPS ≥1.

PASC previously noted there is no reference standard.

Rationale

The key randomised trial cited in the Application Form (KEYNOTE-048) enrolled patients with recurrent or metastatic HNSCC (including those who were PD-L1 positive and negative, i.e., all-comers) and provides a comparison of:

- pembrolizumab monotherapy;
- pembrolizumab in combination with a platinum-based drug (cisplatin or carboplatin) plus 5-FU; and
- cetuximab plus a platinum-based drug (cisplatin or carboplatin) plus 5-FU.

The EXTREME regimen (a combination of cetuximab, platinum-based chemotherapy, and 5-FU) is the only regimen in the National Comprehensive Cancer Network (NCCN) guidelines to have Category 1 evidence. Other regimens recommended in the NCCN guidelines include combination regimens of platinum plus a taxane, cisplatin plus cetuximab and cisplatin plus 5-FU or these agents as monotherapies. The current PBS listing of cetuximab is limited to "Stage III, IVa or IVb squamous cell carcinoma of the larynx, oropharynx or hypopharynx", thus not all HNSCC; and can only be used in combination with radiotherapy and in patients unable to tolerate cisplatin (thus the treatment used in a proportion of patients in the comparator arm of KEYNOTE-048 trial may not be applicable to Australia). Although the use of cetuximab plus chemotherapy in HNSCC was considered at the March

2018 PBAC meeting and recommended for listing on the PBS[1], advice from the applicant indicated that it will not be PBS listed, and therefore it will not be a relevant comparator. The comparator (cetuximab plus a platinum-based drug (cisplatin or carboplatin) plus 5-FU) in the KEYNOTE-048 trial is unlikely to be representative of standard of care and an indirect comparison to 'platinum plus 5-FU' or a taxane will be required for the integrated codependent submission.

The nominated comparator of no PD-L1 testing is considered appropriate. However, given the availability and potential use of other PD-L1 testing kits; another relevant comparison is the PD-L1 IHC 22C3 pharmDx assay versus other PD-L1 antibodies or testing assays, whilst also accounting for any concomitant variation in choice of platform or scoring approach.

PASC confirmed that the proposed comparator for the test was appropriate, and that the analytical performance of relevant test options (assays and platforms) available in Australia should be compared with that of the PD-L1 assay and platform used in KEYNOTE-048.

OUTCOMES

Patient-relevant outcomes

Safety outcomes

- Adverse events relating to tolerability and toxicity of pembrolizumab treatment.

Test-related outcomes

- Efficacy and safety outcomes of pembrolizumab treatment with and without prior PD-L1 testing; and
- Psychological and physical harms from testing (including rates of re-biopsy and re-testing).

Treatment-related outcomes

- Overall survival;
- Disease-specific survival;
- Progression-free survival;
- Time to progression;
- Rate of recurrence;
- Time to recurrence;
- Overall response rate;
- Duration of response; and
- Quality of life

Test outcomes

- Trial-based PD-L1 IHC assay analytical performance;
- Comparative performance of PD-L1 testing methods (the applicant noted that this is not being conducted as part of the KEYNOTE-048 trial); and
- Re-testing rates.

[1] Cetuximab Public Summary Document

Cost-effectiveness outcomes

- Cost per life year gained; and
- Cost per QALY gained.

Healthcare resource outcomes

- Cost of testing per case;
- Re-biopsy rates;
- Test turn-around time;
- Estimated number of patients tested;
- Net cost to the Medicare Benefits Schedule (MBS); and
- Net cost to the Pharmaceutical Benefits Scheme (PBS).

Rationale

In patients with HNSCC, higher PD-L1 expression has been shown to be predictive of poorer prognosis (Lin et al 2015). The integrated codependent submission should explicitly demonstrate this relationship. The approach to presenting the evidence may differ according to the available evidence (i.e. direct evidence or linked evidence) (see Figure P4.1 and Section 2 – Clinical Evaluation, Subsection P4.2 of Product Type 4 of the Guidelines for preparing a submission to the PBAC).

The key clinical trial, KEYNOTE-048 presented in the list of evidence in Section 4 of the application, has been analysed based on outcomes in patients with PD-L1 positive expression and based on outcomes in all patients regardless of PD-L1 expression. It is expected that PD-L1 testing will help to determine the most appropriate clinical pathway for an individual patient, with the trial results indicating that a patient is more likely to respond better to the PD-1 inhibitor pembrolizumab if a patient has a CPS score ≥1, in comparison with the current standard of care.

The following outcomes could also be included:

Biomarker

- The prognostic effect of PD-L1 expression in patients with recurrent (not amenable to local treatment) or metastatic HNSCC, irrespective of the clinical management provided.

Test

- Effectiveness:
  - Analytic performance: precision of the test; and
  - Clinical utility: outcomes from treatment with and without PD-L1 testing, relative to standard of care.
- Change in management: whether knowledge of the test result will result in a change in the management of the patient by the treating clinician.
- Predicted use of the test and medicine in practice:
  - Estimated number of patients treated;
  - Number of patients tested per PD-L1 positive result; and
  - Number of patients tested per PD-L1 positive result treated with pembrolizumab monotherapy.

PASC confirmed the proposed outcomes.

Current and proposed clinical management algorithms

*PASC advised that the second box in the clinical management algorithms should be amended to specify 'who are **not** amenable to local treatment'.* This was updated accordingly in the clinical algorithms presented below.

PASC noted and agreed with the applicant's advice that the clinical management algorithms should also include nivolumab as a management option, which is PBS listed after progression within 6 months of prior platinum based chemotherapy in recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx. Both the current and proposed clinical management algorithms were updated to include nivolumab.

The applicant advised that the clinical management algorithm has been amended in the codependent technology submission. However, it noted that that nivolumab will not be positioned after pembrolizumab, since the current PBS restriction for nivolumab prevents its use after a prior PD-1 inhibitor.

Current clinical management algorithm for identified population

The application stated that currently, patients with recurrent or metastatic disease do not undergo PD-L1 testing and are offered either palliative (platinum-based) chemotherapy-based regimens as both a first- and second-line of treatment or best supportive care. Which treatment or combination of treatments they receive will depend on their general state of health, performance status, and what they have previously received. Recently, nivolumab has become an alternative management option, which is PBS listed for those who experience progression within 6 months of prior platinum based chemotherapy in recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx. Nivolumab would not be used after pembrolizumab as the PBS-listing for initiation of treatment with nivolumab states "Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor for this condition".

Figure 2 summarises the current clinical pathway for patients with suspected recurrent or metastatic HNSCC as depicted in the application and *amended to include nivolumab as second-line after platinum-based chemotherapy)*. It is not clear that the current clinical pathway as depicted in the application is representative of current clinical management. In the first- and second-line settings, patients may also receive targeted therapies or the EXTREME regimen (a combination of cetuximab, platinum-based chemotherapy, and 5-FU).

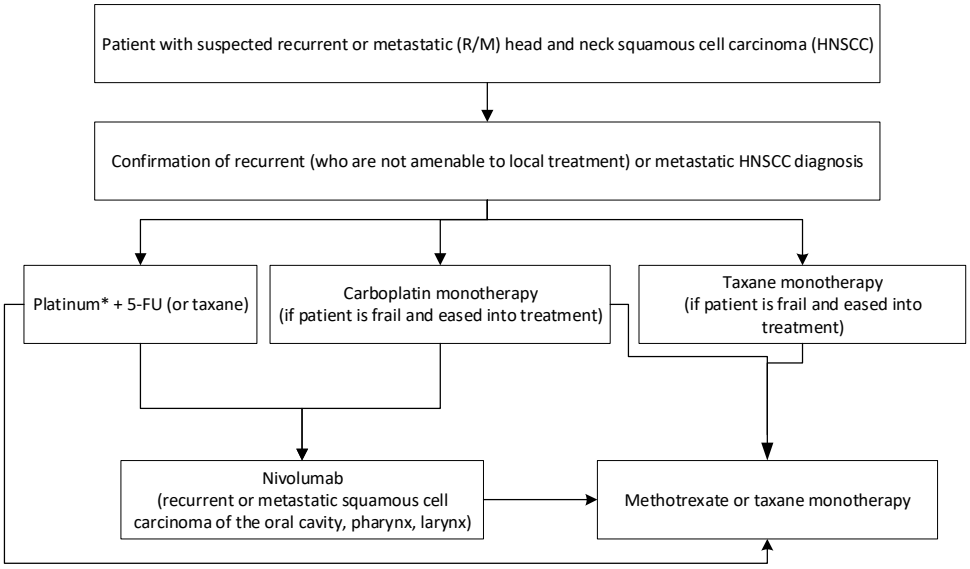

Figure 2: Current clinical treatment algorithm for recurrent or metastatic squamous-cell carcinoma of the head and neck (HNSCC) in the absence of PD-L1 testing

HNSCC = head and neck squamous cell carcinoma; 5-FU = 5-fluorouracil

* Carboplatin in patients who cannot tolerate cisplatin

Proposed clinical management algorithm for identified population

Figure 3 summarises the ways in which the applicant predicted that the treatment algorithm for patients with recurrent or metastatic HNSCC would likely change with the MBS listing of PD-L1 testing and PBS listing of pembrolizumab for this indication, *amended to include treatment with nivolumab. As for the current algorithm presented in Figure 2, PASC noted that in the first- and second-line settings, patients may also receive targeted therapies or the EXTREME regimen (a combination of cetuximab, platinum-based chemotherapy, and 5-FU).*

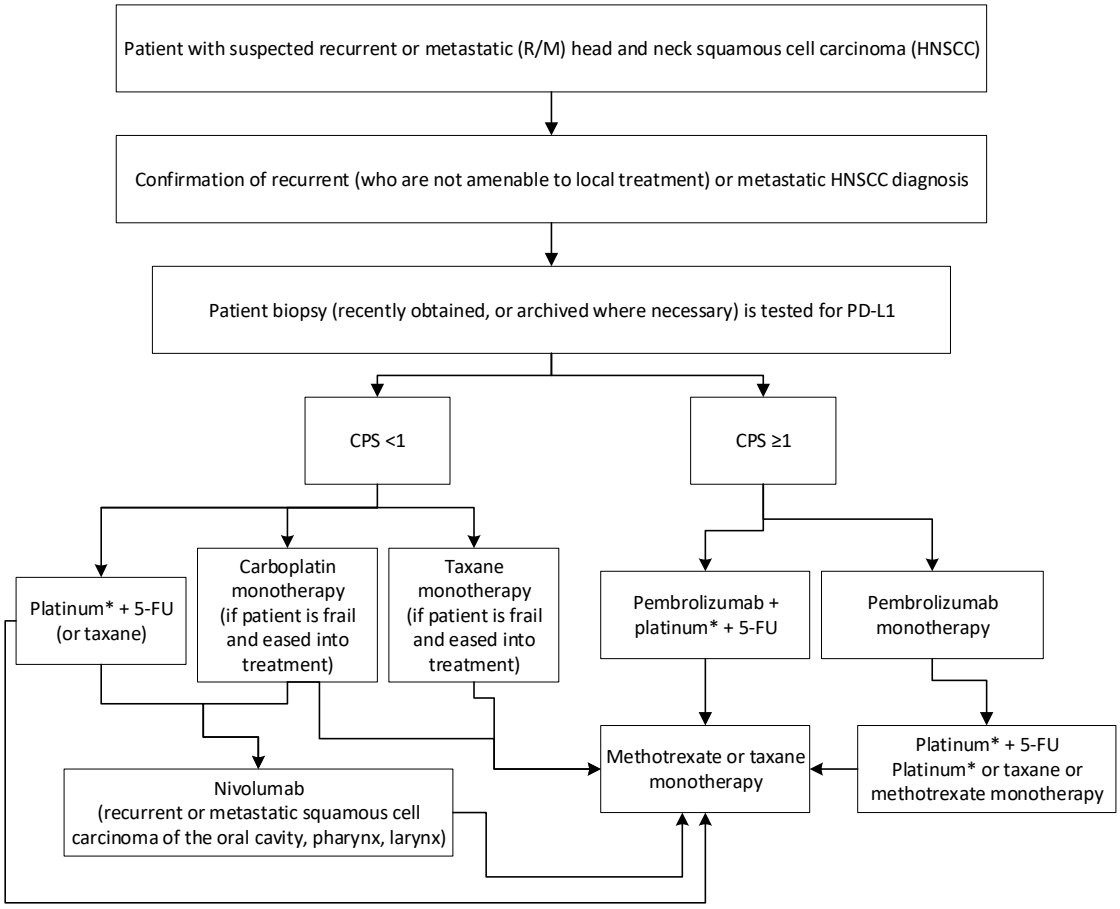

Figure 3: Proposed clinical treatment algorithm for recurrent or metastatic squamous-cell carcinoma of the head and neck (HNSCC) with PD-L1 testing

HNSCC = head and neck squamous cell carcinoma; 5-FU = 5-fluorouracil; PD-L1 = programmed cell death-ligand 1; CPS = combined positive score.

* Carboplatin in patients who cannot tolerate cisplatin

Proposed economic evaluation

A claim of superiority compared with current standard of care is proposed. On the basis of this claim, the appropriate type of economic evaluation would be a cost-utility analysis (or cost-effectiveness analysis).

PASC previously noted an economic evaluation should also present incremental cost-effectiveness ratios, compared to no PD-L1 testing and standard of care, for the following scenarios:

1. PD-L1 testing and pembrolizumab treatment in patients who express PD-L1 (and therefore, standard of care in those that do not); and
2. Pembrolizumab treatment (monotherapy or combination therapy) in all patients (i.e. no PD-L1 testing).

If evidence presented supports that pembrolizumab results in superior health outcomes (and is acceptably cost-effective compared to the standard of care) in patients who do and do not express PD-L1, then PD-L1 testing will not provide additional utility.

PASC confirmed the proposed approach to the economic evaluation.

Proposed MBS item descriptor and MBS fee

Category 6 – Pathology Services
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 or recurrent (untreatable by local therapies) squamous cell carcinoma of the head and neck, to determine if the requirements relating to PD-L1 status for access to pembrolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $74.50 75% = $55.90 85% = $63.35

The applicant stated that the proposed fee is the same as that for MBS item 72814 for PD-L1 testing for NSCLC.

PASC confirmed the proposed MBS item descriptor and noted the proposed MBS fee. PASC considered that the omission of "first-line" (in reference to pembrolizumab) from the MBS item descriptor was appropriate.

The applicant advised that it has amended the MBS item number *for the codependent submission to include the 22C3 antibody only, due to lack of evidence to support use of other antibodies.*

Consultation feedback

PASC noted the consultation feedback.

PASC previously noted the following targeted consultation feedback:

- *Royal College of Pathologists of Australasia (RCPA)*: While supporting this application (1522), the respondent highlighted previously-raised issues about the imperfect nature of PD-L1 IHC as a predictive biomarker for selecting patients likely to respond to immunotherapy. They also highlighted challenges associated with different scoring algorithms for different tumour types, and inter-operability of assays. Despite this, they acknowledge there is no clear alternative assay or gold standard, and it is the best test currently available.
- *Specialist / medical oncologist* — Peter MacCallum Cancer Centre, Melbourne: Supports the application, but declared a conflict of interest as an investigator in KEYNOTE-048.

PASC noted the additional clinical statement of support provided 26 March 2020:

- RCPA: *While supporting this application (1522), the RCPA noted 'In the head and neck, the combined positive score is a useful PD-L1 scoring method' of PD-L1 testing to assist in selecting patients who may benefit from immunotherapy. RCPA noted 'the importance of Quality Assurance Programs (QAP) and accurate training in the diagnostic evaluation of PD-L1 positivity in this context. The assessment of PD-L1 is challenging in existing testing contexts, as it can suffer from variability and ambiguities in interpretation. Multiple PD-L1 antibodies are available. There is also variation in the affinity and staining intensity of the tumour cells and immune infiltrate. However, this can be managed with a high standard of training and QAP involvement.'*

Other issues

PASC previously recommended the following clinical issues be considered:

- The different criteria for (subsidised) access to pembrolizumab in other indications;
- The different definitions for interpretation of PD-L1 positivity/thresholds for access. The applicant has sought clarification as to whether this is referring to (i) why are there different definitions; (ii) what the definitions are; or (iii) something else?
- The variety of PD-L1 assays in the literature and funding submissions. Is there still an ongoing need for sensitivity/specificity comparisons, in the absence of a gold standard?
- Whether there is a relationship between PD-L1 and clinical response to pembrolizumab (and other PD-L1 agents)?

PASC requested that the issues around archival and fresh tissue be resolved clearly within the PICO.

The applicant noted that the vast majority of testing will be done on newly obtained tissue. The applicant advised that in the codependent technology submission, evidence is presented demonstrating no difference in scoring of archival vs newly obtained tissue.

Summary of discussion

In its first consideration of Application 1522 (April 2018), PASC discussed the ongoing challenge of comparative clinical validity of testing platforms. However, PASC acknowledged that the applicant's advice (that scoring systems and thresholds will vary according to tumour-type) provided some clarity on this issue.

Next steps

Following its second consideration of Application 1522 (April 2020), PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant elected to progress its application as an ADAR (applicant-developed assessment report) in the form of an integrated codependent submission.

The applicant advised the submission will be lodged in June 2020.

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