Australian Government

Department of Health

Application 1457:

PD-L1 (Programmed Death-Ligand 1) immunohistochemistry testing for access to pembrolizumab as first-line therapy for patients with locally advanced or metastatic urothelial cancer ineligible for cisplatin-based therapy.

PICO Confirmation

(to guide a new application to MSAC)

December 2016

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	Patients with a diagnosis of locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-based therapy
Prior tests	Routine histology, cytology and immunohistochemistry tests to confirm diagnosis of locally advanced or metastatic urothelial cancer
Intervention	PD-L1 testing to identify patients who express PD-L1 for access to pembrolizumab treatment
Comparator	No PD-L1 testing and treatment with standard of care: carboplatin + gemcitabine, carboplatin or gemcitabine monotherapy or best supportive care
Outcomes	**Biomarker** • Prognostic effect of PD-L1 expression in patients with locally advanced or metastatic urothelial cancer • Pembrolizumab treatment effect modification by PD-L1 expression **Test** • Safety: psychological and physical harms from testing (including rates of re-biopsy and re-testing) • Effectiveness o Analytic performance: precision o Comparative performance: concordance with other tests that predict a response to anti-PD-L1 therapies o 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 causes a change in the management of the patient by the treating clinician **Medicine** • Safety: adverse events related to a change in treatment including tolerability and toxicity (particularly immune-related adverse events) • Effectiveness o Primary: overall survival; quality of life; progression free survival o Secondary: response rate (complete response or partial response according to RECIST and irRC criteria); disease control rate (response rate + rate of stable disease); duration of response; rate of disease progression; time to progression **Co-dependent technologies** • Clinical utility: outcomes from treatment with and without PD-L1 testing, relative to standard of care • Cost-effectiveness

Component	Description
	○ PD-L1 testing and pembrolizumab treatment compared to no PD-L1 testing and standard of care treatment: cost per quality-adjusted life year gained; cost per life year gained; cost of testing per PD-L1 positive case detected; cost of testing per PD-L1 positive case detected and treated with pembrolizumab ○ pembrolizumab treatment in an unselected population, compared to no PD-L1 testing and standard of care treatment: cost per quality-adjusted life year gained; cost per life year gained • Predicted use of the test and medicine in practice ○ Number of patients tested ○ Number of patients treated ○ Number of patients tested per PD-L1 positive result ○ Number of patients tested per PD-L1 positive result treated with pembrolizumab ○ Financial implications for the MBS ○ Financial implications for the PBS ○ Financial implications for the Australian Government

Research questions

- What is the safety, effectiveness and cost-effectiveness of PD-L1 testing for access to pembrolizumab compared to no PD-L1 testing and standard of care treatment?
- What is the safety, effectiveness and cost-effectiveness of pembrolizumab treatment without PD-L1 testing compared to no PD-L1 testing and standard of care treatment?

Linked evidence

- What is the analytic and comparative performance of PD-L1 testing for determining access to pembrolizumab in patients with locally advanced or metastatic urothelial cancer?
- Is PD-L1 testing able to predict differences in health outcomes in patients with locally advanced or metastatic urothelial cancer irrespective of clinical management provided?
- Is there a change in management in patients with locally advanced or metastatic urothelial cancer who are found to express PD-L1?
- Is there a treatment effect modification (i.e. interaction) as a consequence of biomarker status?
- Does treatment with pembrolizumab lead to better health outcomes in patients with locally advanced or metastatic urothelial cancer who express PD-L1 compared with standard of care treatment?
- Is PD-L1 testing safe in patients with locally advanced or metastatic urothelial cancer compared with no testing?

PICO rationale

Population

The target population for programmed death-ligand 1 (PD-L1) testing is proposed to be patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-based therapy, on diagnosis of advanced disease. Pembrolizumab treatment is proposed in patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-based therapy and who are found to express PD-L1.

Urothelial cancers most commonly present in the bladder, but can also present in the ureters or renal pelvis. More than 90% of all bladder cancers are urothelial subtype. Bladder cancer accounts for approximately 2% of all new cancers in Australia with approximately 2,800 patients diagnosed each year. The Application Form indicates that approximately 38% have locally advanced or metastatic disease. However, the majority of advanced cases would have relapsed from an earlier stage of disease and so PD-L1 testing would most likely occur on archival tissue samples from these patients.

Approximately 50% are ineligible for cisplatin, due predominantly to renal dysfunction, poor performance status and/or co-morbidity.[1] Patients with at least one of the following are considered ineligible for cisplatin (as per eligibility criteria for KEYNOTE-052, KN-052):

- Eastern Cooperative Oncology Group (ECOG) performance status of 2;
- Renal dysfunction (creatinine clearance < 60 mL/min but ≥30 mL/min);
- Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 audiometric hearing loss or peripheral neuropathy; or
- New York Heart Association (NYHA) class III heart failure.

Prevalence of PD-L1 expression from interim analysis of the first 100 patients enrolled in KN-052 observed that 63% showed any PD-L1 expression (defined as ≥1% combined positive score, CPS) and that 30% had high PD-L1 expression, defined as ≥10% CPS.[2] The Application From noted that prevalence of PD-L1 expression (≥1% scoring method not reported) in KEYNOTE-012 (KN-012), was 64.2%.

Rationale

The Application Form lists two studies as supporting evidence, KN-052 and KN-012. KN-052 is a single-arm, phase 2 study of pembrolizumab as first-line therapy for adults with locally advanced or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra who are ineligible for cisplatin. Patients were enrolled into KN-052 on a PD-L1 'all-comers' basis. KN-012 is a single-arm, phase 1b study of pembrolizumab, any line, for adults with advanced urothelial cancer of the bladder, renal pelvis, ureter, or urethra. Patients who showed ≥1% PD-L1 expression in tumours cells

[1] Bellmunt J., Orsola A., Leow J.J., et al. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2014, 25 Suppl 3, iii40-8.

[2] Balar, A., Bellmunt, J., O'Donnell, P.H., et al. Pembrolizumab (pembro) as first-line therapy for advanced/unresectable or metastatic urothelial cancer: Preliminary results from the phase 2 KEYNOTE-052 study, *Ann Oncology*, 2016, 27, Suppl 6. Available from: Ann Oncology, 2016, 27, Suppl 6

or a PD-L1–positive band in stroma by a prototype immunohistochemistry assay were enrolled. *The proposed population is consistent with the population enrolled in KN-052.*

The approach of limiting the test only to those with locally advanced or metastatic disease who are ineligible for cisplatin-based therapy may introduce inefficiencies related to the timing of the test, as this approach would unlikely be pathologist-determinable, as proposed. However, pathologists may not know the disease stage of the patient when performing routine tests to confirm the diagnosis of urothelial cancer (i.e. whether cancer is locally advanced or metastatic), which may limit the extent to which the test is pathologist-determinable.

The Application Form indicates that leakage in populations not targeted by the service would be minimal. *There is potential for leakage of testing in patients who are eligible for cisplatin-based therapy, in patients at earlier stages of urothelial cancer (particularly if pathologists do not know the disease stage of the patient) or testing in other indications. Testing patients who are eligible for cisplatin may result in leakage of pembrolizumab use in patients who are able to tolerate cisplatin and who are found to express PD-L1. This use is being explored in a randomised phase 3 clinical trial, KEYNOTE-361, which began enrolling in September 2016 and has an estimated primary completion of March 2019)*[3]*. Patients are being enrolled in this trial on a PD-L1 'all-comers' basis. Further, patients who are ineligible for cisplatin therapy may also be enrolled in KEYNOTE-361 as participants randomised to the comparator arm receive either cisplatin + gemcitabine or carboplatin + gemcitabine. However it is unclear whether cisplatin-eligibility is a stratification factor.*

Prior test (investigative services only - if prior tests are to be included)

Prior tests include those to confirm the diagnosis and histological subtype of locally advanced or metastatic urothelial cancer.

Intervention

The intervention is PD-L1 testing and selective treatment with pembrolizumab for those with PD-L1 expression, and standard of care for those without PD-L1 expression. Pembrolizumab is a highly selective humanised monoclonal antibody that targets the PD-L1 receptor to elicit an immune response. PD-L1 expression in urothelial cancer tumour biopsies can be assessed using immunohistochemistry (IHC) testing with antibodies that bind specifically to the PD-L1 protein.

The PD-L1 assay used in studies of pembrolizumab in urothelial cancer is the Dako PD-L1 IHC 22C3 pharmDx Market Ready Assay, and takes between 2.5-4 hours depending on instrumentation and protocol used. This assay was used to assess PD-L1 expression in urothelial cancer tumour biopsies in the KN-052 study. Limited information is presented in the Application Form regarding the test and IHC scoring methodology. However, the Application for PD-L1 testing and pembrolizumab treatment for second-line advanced/metastatic bladder cancer (Application 1445) proposed using the CPS, which scores both inflammatory cells and tumour cells which is different to the proposed use of PD-L1 testing in non-small cell lung cancer (NSCLC; tumour proportion score, TPS), which scores only tumour cells. This scoring approach was chosen as, in the case of urothelial cancer, incorporating PD-L1 expression in inflammatory cells could help improve the performance of the test. *PASC may wish*

[3] ClinicalTrials.gov Identifier: NCT02853305, Study of Pembrolizumab With or Without Platinum-based Combination Chemotherapy Versus Chemotherapy Alone in Urothelial Carcinoma (MK-3475-361/KEYNOTE-361)

to consider whether PD-L1 testing in the first-line urothelial cancer setting should be aligned with that proposed in the later-line setting (Application 1445), in terms of scoring approach and cut-offs for determining eligibility to pembrolizumab.

Therapeutic Goods Administration (TGA) registration of this test is pending and there are no other PD-L1 tests commercially available in Australia, nor is PD-L1 testing listed on the Medicare Benefits Schedule (MBS) for any indication. Applications are in progress for MBS listing of PD-L1 testing for access to pembrolizumab in other indications (Application 1414 and 1440 for NSCLC, and Application 1445 for second-line advanced/metastatic bladder cancer). Pembrolizumab is listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of melanoma, however this listing does not restrict by PD-L1 status.

The Application Form indicates that only one test per patient is likely to be required through the course of disease. *It may be useful for the submission to present evidence to support whether or not PD-L1 status changes in response to prior treatment exposure. Patients who are found not to be eligible for first-line treatment with pembrolizumab may be eligible for pembrolizumab after disease progression following platinum-based chemotherapy (see Application 1445). If there is the potential for PD-L1 status to change in response to prior treatment, then these patients may require a re-biopsy and an additional PD-L1 test to determine eligibility to later-line pembrolizumab.*

The proposed MBS item descriptor does not restrict PD-L1 testing by assay (i.e. does not specify that the Dako 22C3 PD-L1 test assay be used to determine eligibility to pembrolizumab). *Other PD-L1 IHC assays or alternative tests that predict a response to anti-PD-L1 therapies may be eligible for use. It may be useful for the submission to present evidence to support the clinical utility of alternative testing methods for identifying patients eligible for pembrolizumab.*

It is proposed that the test be pathologist-determinable, however the Application Form indicates that specialists, including urologists and oncologists, may provide a referral for PD-L1 testing. The Application Form proposes 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.

It is proposed that PD-L1 IHC testing be performed in any pathology laboratory holding appropriate accreditation to claim pathology services through the MBS. The Application Form states 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*.

The Application Form indicates that uptake of PD-L1 testing in the proposed population would be high (100%). Justification for this was that if KN-052 (a single arm phase 2 study) indicates that patients who express PD-L1 benefit more from pembrolizumab than those who do not express PD-L1, then pembrolizumab could replace non-cisplatin chemotherapies as standard of care in patients who express PD-L1, and uptake of PD-L1 testing would be 100% for all patients diagnosed with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-based therapy.

Uptake of testing is likely to depend on the comparative effectiveness and safety of pembrolizumab to non-cisplatin chemotherapies 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, as without a comparison to non-cisplatin chemotherapies by PD-L1 status, the difference in effect could be due to treatment effect modification and/or due to the prognostic effect of the biomarker.

The Application Form has not nominated a reference standard or evidentiary standard against which to compare proposed PD-L1 testing. *As the assay used in the KN-052 study is the same assay to be made commercially available, then the intervention is the evidentiary standard. If the test performs in clinical practice as per the clinical study, then the implications of false positives and false negatives are directly inherent in the outcomes data of the study. Concordance of alternative tests that predict a response to anti-PD-L1 therapies with the evidentiary standard would also need to be provided.*

The Application Form 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.*

Rationale

PASC may wish to consider whether an optimal PD-L1 expression cut-off that predicts the clinical benefit of pembrolizumab (or of other PD-L1 or PD-1 inhibitors) is needed. Analyses of treatment effect variation based on mutually exclusive subsets of PD-L1 expression (for example <1% vs. ≥1% to <5% vs. ≥5% to <10% vs. ≥10% etc.) could be useful for MSAC and PBAC consideration as it would allow the impact of increasing levels of expression on the comparative effectiveness of pembrolizumab to be elucidated.

Comparator

The primary comparator is no PD-L1 testing and current standard of care (carboplatin + gemcitabine or gemcitabine or carboplatin monotherapy). In those who are unable to tolerate current standard of care, the comparator of treatment may be best supportive care.

PD-L1 testing is proposed to be used in addition to current tests used to confirm the diagnosis of locally advanced or metastatic urothelial cancer.

Pembrolizumab is proposed to replace current standard of care (carboplatin + gemcitabine or gemcitabine or carboplatin monotherapy) in patients who are found to express PD-L1 and are ineligible for cisplatin-based treatment. *However, the introduction of pembrolizumab may shift or delay access to the comparator rather than replace it, as patients may still receive the comparator after progressing on pembrolizumab treatment*.

Rationale

Neither of the studies listed as supportive evidence in the Application Form enrolled a comparator arm. However, the nominated comparator for pembrolizumab treatment in this setting is consistent with European Society of Medical Oncology (ESMO) and National Institute for Health and Care

Excellence (NICE) guidelines for the treatment of urothelial cancer who are ineligible for cisplatin, which recommend carboplatin + gemcitabine as the preferred treatment option.[4,5]

Outcomes

Patient relevant

Testing

- Psychological and physical harms from testing (including rates of re-biopsy and re-testing)

Treatment

- Any adverse events related to a change in treatment including tolerability; toxicity (particularly immune-related adverse events).
- Primary effectiveness outcomes: Overall survival; quality of life; progression free survival
- Secondary effectiveness outcomes: response rate (complete response or partial response according to Response Evaluation Criteria in Solid Tumors [RECIST] and immune-related Response Criteria [irRC] criteria); disease control rate (response rate + rate of stable disease); duration of response; rate of disease progression; time to progression.

Healthcare system

Cost-effectiveness

- PD-L1 testing and pembrolizumab treatment compared to no PD-L1 testing and standard of care treatment (as appropriate): cost per quality-adjusted life year gained; cost per life year gained; cost of testing per PD-L1 positive case detected; cost of testing per PD-L1 positive case detected and treated with pembrolizumab
- pembrolizumab treatment in an unselected population, compared to no PD-L1 testing and standard of care treatment (as appropriate): cost per quality-adjusted life year gained; cost per life year gained

Predicted use of the test and medicine in practice

- Number of patients tested
- Number of patients treated
- Number of patients tested per PD-L1 positive result
- Number of patients tested per PD-L1 positive result treated with pembrolizumab
- Financial implications for the MBS
- Financial implications for the PBS

Rationale

Co-dependent submissions should explicitly demonstrate the relationship between the test for the biomarker and the medicine, such that it is clear whether treatment effect modification and/or a

[4] Bellmunt J., Orsola A., Leow J.J., et al. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2014, 25 Suppl 3, iii40-8.
[5] NICE Guidelines [NG2], February 2015: Bladder cancer: diagnosis and management

prognostic effect is operating in the relationship. The approach to presenting evidence in a co-dependent submission 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 following outcomes could also be included:

Biomarker

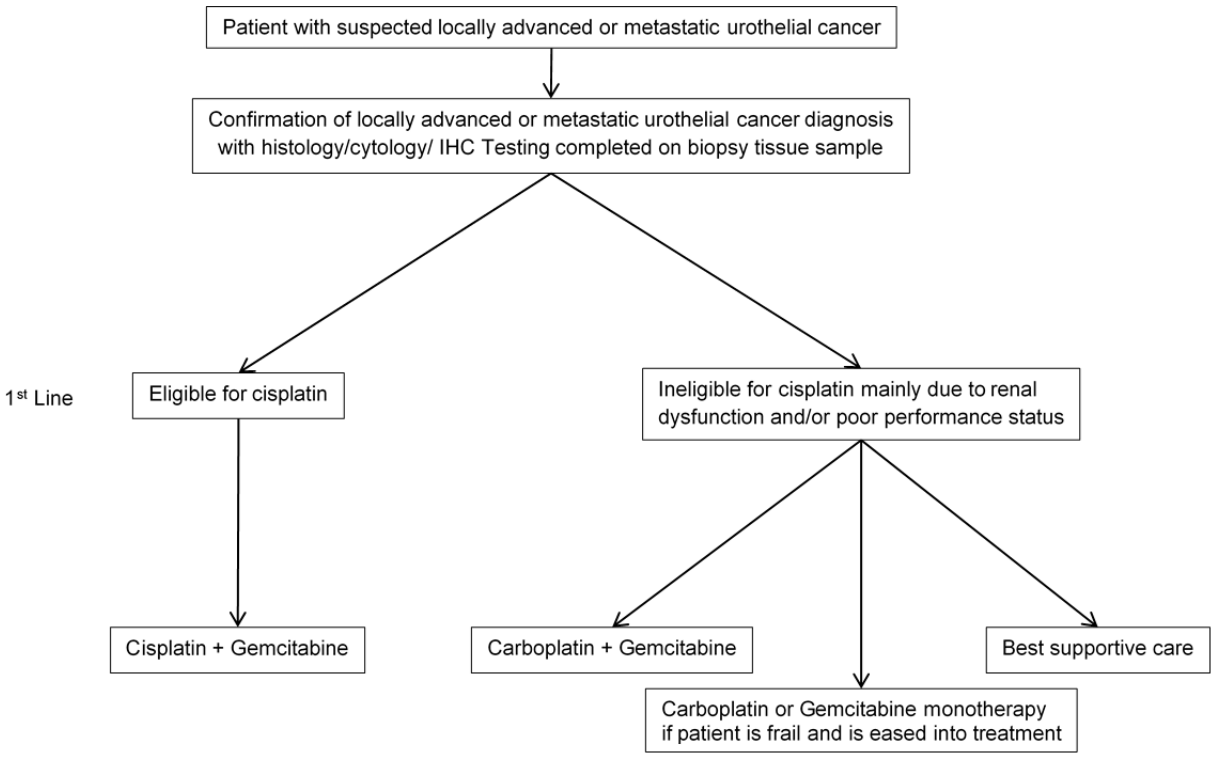
- *The prognostic effect of PD-L1 expression in patients with locally advanced or metastatic urothelial cancer, irrespective of the clinical management provided*

Test

- *Effectiveness:*
  - *Analytic performance: precision of the Dako 22C3 PD-L1 test*
  - *Comparative performance: concordance of the Dako 22C3 PD-L1 test with other PD-L1 assays and tests that predict a response to anti-PD-L1 therapies*
  - *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 cause a change in the management of the patient by the treating clinician.*

Current clinical management algorithm for identified population

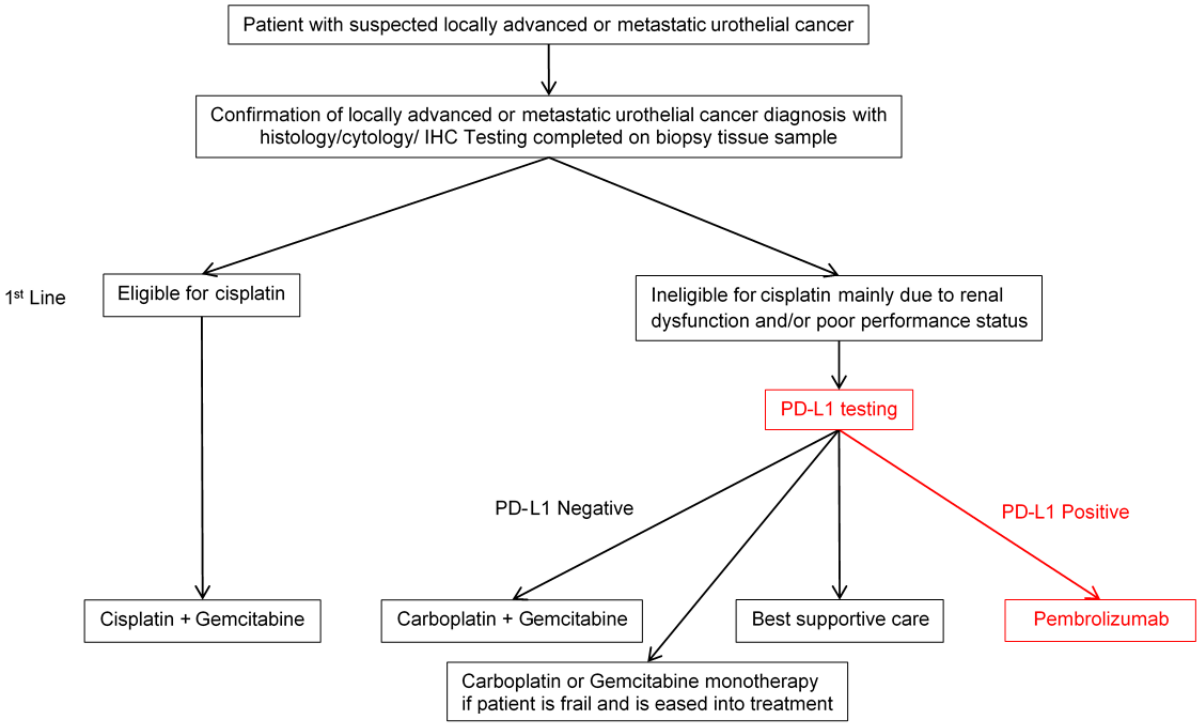
The current clinical management algorithm is shown below.



IHC = immunohistochemistry

Proposed clinical management algorithm for identified population

The proposed clinical management algorithm is shown below. *The proposed management algorithm has been amended from that presented in the Application Form upon clarification of the proposed population eligible for testing (i.e. only those patients who are ineligible for cisplatin-based therapy).*



IHC = immunohistochemistry; PD-L1 = programmed death-ligand 1.

Proposed economic evaluation

A claim of superiority is presented in the Application Form, based on the claims of acceptable safety and analytical performance of PD-L1 testing and superior effectiveness and acceptable safety of treating patients who express PD-L1 with pembrolizumab relative to standard of care. *On the basis of this claim, the appropriate type of economic evaluation would be a cost-utility analysis. However, comparative evidence of PD-L1 testing or pembrolizumab treatment is not included in the preliminary supporting evidence identified in Part 4 of the Application Form. Additional evidence will need to be presented in order to substantiate these claims.*

In order to assess the cost-effectiveness of the co-dependent technologies, it may be useful for the submission to 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 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.

Proposed item descriptor

The MBS item number proposed by the Applicant is shown below.

Category 6 – Pathology Services
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)

PASC may wish to consider whether the proposed item descriptor should specify the proposed population eligible for PD-L1 testing (i.e. patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-based therapy) in order to prevent utilisation in other indications.