



Australian Government

Department of Health

Application 1506:

Programmed cell death ligand 1 (PD-L1) testing to determine PBS access to durvalumab or durvalumab/tremelimumab as 1st line therapy for patients with unresectable Stage IV urothelial cancer

PICO Confirmation

(To guide a new application to MSAC)

(Version 1.0)

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 and Drug: Patients with unresectable stage IV urothelial cancer, previously untreated for Stage IV disease
Prior tests	Routine imaging, cytology, cystoscopy and histology work-up to confirm diagnosis of unresectable Stage IV urothelial cancer.
Intervention	<p>Test: Immunohistochemistry (IHC) assay to determine high PD-L1 expression versus low PD-L1 expression in tumour tissue.</p> <p>Drug(s):</p> <ul style="list-style-type: none"> • Durvalumab monotherapy (high PD-L1 patients) or; • Durvalumab + tremelimumab combination therapy (low/no PD-L1 patients). <p>Co-dependence: Access to durvalumab or durvalumab + tremelimumab in patients who fulfil the PBS requirements for PD-L1 status, determined by PD-L1 IHC testing.</p> <p>Supplementary comparison: PD-L1 testing + durvalumab in those with high PD-L1.</p>
Comparator	<p>Test: No PD-L1 testing</p> <p>Drug(s): standard of care, which is platinum-based chemotherapy (either cisplatin + gemcitabine or carboplatin + gemcitabine depending on suitability for cisplatin).</p> <p>Near comparator: PD-L1 testing + pembrolizumab in high PD-L1 patients.</p>
Outcomes	<p>TEST OUTCOMES – in brief (see Outcomes section for details)</p> <p>Safety</p> <p>Clinical Effectiveness</p> <p>Trial based (evidentiary standard) PD-L1 IHC assay analytical performance</p> <p>Comparative performance of PD-L1 testing methods</p> <p>Clinical utility of test</p> <p>Other test-related considerations</p> <p>DRUG OUTCOMES – in brief (see Outcomes section for details)</p> <p>Safety</p> <p>Clinical Effectiveness</p> <p>Co-primary outcomes</p> <p>Secondary outcomes</p> <p>Exploratory outcomes</p>

Research Questions

What is the safety, effectiveness, and cost-effectiveness of IHC PD-L1 testing for determining access to durvalumab monotherapy or durvalumab + tremelimumab combination therapy, as first line treatment, in patients with unresectable stage IV urothelial cancer, compared with no testing and standard of care (platinum-based chemotherapy)?

What is the safety, effectiveness, and cost-effectiveness of no PD-L1 testing and durvalumab monotherapy or durvalumab + tremelimumab combination therapy, as first line treatment, compared to no testing and standard of care in patients with unresectable stage IV urothelial cancer?

Also:

Does the PD-L1 test result predict a treatment effect modification with these particular PD-1 inhibitors (durvalumab and/or durvalumab + tremelimumab)

What are the analytical performance characteristics of the proposed PD-L1 test in the applicant's clinical trial? How will this translate to Australian pathology practice?

Is the PD-L1 test safe in the test-eligible population compared with no testing?

What are the consequences for patients with false low PD-L1 or false high PD-L1 results receiving the incorrect treatment?

Is the difference in PD-L1 status based on this test associated with any difference in prognosis, irrespective of treatment given?

Population

The applicant proposes patients with unresectable Stage IV urothelial cancer, for treatment with PBS durvalumab, or PBS durvalumab + tremelimumab, as first line therapy. Thus the population is "Patients with unresectable stage IV urothelial cancer, previously untreated for Stage IV disease".

This is the same indication that will be sought from the Therapeutic Goods Administration (TGA) (May 2018 lodgement planned). Elsewhere, AstraZeneca recently received regulatory approval from the United States Food and Drug Administration (FDA) for durvalumab monotherapy, for later line treatment in the broader population of "patients with locally advanced or metastatic urothelial carcinoma" (1 May 2017), though this is a breakthrough therapy designation/accelerated approval based on limited clinical data². The sponsor's TGA submission (and to PBAC/MSAC) will be based on a different and more recent Phase III 'DANUBE' clinical trial (NCT02516241).

¹ Common abbreviations used in this document: MSAC – Medical Services Advisory Committee; PBAC – Pharmaceutical Benefits Advisory Committee; MBS – Medical Benefits Schedule; PBS – Pharmaceutical Benefits Scheme; PASC – Protocol Advisory Subcommittee; PICO – Population, Intervention, Comparator.

² <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm555930.htm>

The PASC recalled that applications 1445, 1457 and 1440.1 sought MSAC consideration of PD-L1 testing (for pembrolizumab treatment) in similar indications – the final populations ratified by PASC were:

- Application 1457: Patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-based therapy (that is, stage IIIb or IV disease ineligible for cisplatin, first line treatment). *PASC considered this is a near comparator, noting differences in PD-L1 scoring methodology and expression cut-off levels that yield a positive test result.*
- Application 1445: Patients with metastatic or locally advanced/unresectable bladder cancer that has recurred or progressed following platinum-based chemotherapy (that is, stage IIIb unresectable disease and stage IV disease, second line treatment). *This application is now inactive – pembrolizumab in that indication was considered at the PBAC November 2017 meeting without including a requirement for the PD-L1 test.*
- Application 1440.1: *PD-L1 testing for access to pembrolizumab in treatment naïve patients with locally advanced or metastatic non-small cell lung cancer. Although a different population, PASC noted that the outcome of this application, should it lead to listing of a PD-L1 test item, could potentially enable future submissions to proceed as streamlined applications to MSAC.*

Application 1457 refers to locally advanced or metastatic disease, whereas this application refers to stage IV. Regarding terminology, Stage IV disease is interchangeable with ‘metastatic’³. Note that Stage III disease can still include spread to nearby organs such as prostate and vagina.

Reference to ‘unresectable’

The population “patients with unresectable Stage IV urothelial cancer” is the same as for the pivotal DANUBE trial. The Department advises that this qualifier should remain a part of the population. A small proportion of stage IV patients with oligometastatic lung disease (only) may be eligible for potentially curative pulmonary resection. An estimate of the portion such patients represent should be included in the Submission Based Assessment (SBA) to inform utilisation estimates.

PASC should note the difference with application 1457, in which the qualifier ‘unresectable’ was dropped from the population in the final PICO Confirmation.

Urothelial versus bladder cancer

Urothelial cancer and bladder cancer are overlapping – but not identical – terms. Bladder cancer includes some non-urothelial tumours. According to the Urological Society of Australia and New Zealand (USANZ), 90% of bladder cancers are urothelial (transitional cell carcinoma)⁴. The remaining 10% are mostly squamous cell carcinomas and adenocarcinomas, for which treatment options are different⁵. Histological assessment of patients with bladder cancer to differentiate between urothelial cancer and other types is part of the standard diagnostic work-up. Conversely, urothelial cancers include those arising outside the bladder, from the renal pelvis, ureters or urethra. The terms ‘urothelial cancer’ and ‘transitional cell carcinoma of the urothelium’ are interchangeable.

³ Sachintha Hapugoda and Yoshiharu Ryu et al. *Transitional cell carcinoma of the bladder (staging)*. Radiopaedia.

<https://radiopaedia.org/articles/transitional-cell-carcinoma-of-the-bladder-staging-1>

⁴ USANZ Fact Sheet. Bladder Cancer – Transitional Cell Carcinoma. www.usanz.org.au/uploads/65337/ufiles/bladder-cancer.pdf

⁵ Bladder Cancer. US National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2017.

Eligible patients would also include those whose tumours have mixed transitional/non-transitional cell histology.

The applicant has conducted all clinical studies for this treatment in patients with urothelial cancer. Using this tumour type to define the treatment population will ensure access for patients with cancers arising from other urothelial sites who might be excluded from therapy if the population were limited to bladder cancer only. Given that non-urothelial bladder cancers are treated differently, these patients will not be denied treatment by specifying 'urothelial cancer' rather than bladder cancer.

The Australian Institute of Health and Welfare (AIHW) reports bladder cancer statistics but not urothelial cancers of the renal pelvis, ureter and urethra. There are few data that describe the incidence these tumours, though they are expected to be rare (transitional cell carcinoma of the renal pelvis may also be reported as renal tumours).

Other Factors

A brief survey of available guidelines, both local⁶ and international⁷, indicates clinical practice is to differentiate according to non-muscle invasive versus muscle invasive disease. The DANUBE trial will report on invasive versus non-invasive disease status as an assessment at baseline (the SBA should state the proportions of type). The majority of, if not all, patients with stage IV disease are likely to have muscle invasive tumours.

The applicant states that only patients suitable for systemic anticancer therapy will be eligible for testing. Those that are unsuitable constitute approximately 20% of stage IV patients and would normally receive best supportive care – this clinical management will remain unchanged even if the proposed test/treatments are listed. Testing in these patients would be inappropriate.

Patients unsuited to systemic therapy are those with poor performance status and/or comorbidities. This would include patients with a history of heavy smoking and severe comorbidities from chronic airway disease or cardiovascular disease. Comorbidities are common in this group of patients, who have an average age at diagnosis of approximately 75 years (see below).

Test timing

All patients with stage IV urothelial cancer and who meet the criteria below would be eligible for the test. The timing for testing is as follows:

- *After identification of primary tumour(s) of the renal pelvis, ureters, urinary bladder or urethra;*
- *After diagnosis of stage IV disease;*
- *After histological confirmation of urothelial cancer, including tumours of mixed histology;*
- *After having ruled out patients unsuitable for systemic anticancer therapy;*
- *After ruling out patients whose tumours make them candidates for resection;*
- *Prior to selection of first line therapies (precluding any patients who have trialled, or found to be intolerant to, another first line treatment);*

⁶ The Royal Australian College of General Practitioners (RACGP). Ranjan Arianayagam, Mohan Arianayagam and Prem Rashid. *Bladder cancer – Current management*. Australian Family Physician Vol. 40, No. 4, April 2011 209-213.

⁷ NCCN and ESMO Guidelines cited elsewhere in this document; National Institute for Health and Care Excellence (NICE), United Kingdom. *Bladder cancer: diagnosis and management*. NICE guideline 25 February 2015

The PD-L1 test would be ordered for the subset of patients being considered by the specialist for durvalumab monotherapy or combination treatment, once a confirmed diagnosis was in hand and each of the factors above had been considered. This is the test-eligible population. *Patients in this population who have progressed from earlier stage disease would require a re-biopsy to establish PD-L1 expression status.*

After determination of PD-L1 status, patients are divided into two groups– those with high PD-L1 expression and those with no or low PD-L1 expression. These are the treatment-eligible populations. Test negative patients are included in the second population. This test is to determine PBS treatment eligibility and not as a prognostic or diagnostic test of patients at initial diagnosis / presentation. This test is not being proposed for reflex testing.

Prevalence and / or incidence of the population or disease in question

The AIHW reports that in 2013⁸, there were 1957 new bladder cancer cases in men and 598 new cases in women (2555 total). This translates to age-standardised incidence rates per 100,000 of 16.5 men and 4.1 women (9.7 in total), new cases of bladder cancer per year in Australia. The disease is rare in individuals younger than 50 years old. In 2014, mortality due to bladder cancer was 735 deaths in men (age-standardised 6.1 per 100,000 per year) and 305 deaths in woman (age-standardised 1.9 per 100,000 per year). Although incidence is higher in men; survival for women is consistently worse. According to Cancer Australia, bladder cancer has a 5-year relative survival for males of 55.5% but only females of 46.1% (at diagnosis, cases in 2009-2013)⁹. The same data show that the mean age at diagnosis in Australia is 74.4 (males) or 75.6 (females).

The AIHW does not report on this tumour type, thus any available data on incidence of the ‘non-bladder’ urothelial tumours (renal pelvis, ureters and urethra) should be included in the SBA. Nevertheless, if bladder tumours are 90% of urothelial cancers, then based on AIHW figures above:

- All urothelial tumours = 2,174 men; 664 women; or 2,839 total new cases in 2013
- Of which tumours in ureters, renal pelvis and urethra = 217 men; 66 women; or 284 total patients

Without having access to actual cases reported, it is possible that there were up to ~300 incident patients in Australia diagnosed with urothelial tumours of any stage outside the bladder in 2013. Nevertheless, based on a Victorian study of 110 patients with high grade invasive urothelial cancers,¹⁰ bladder tumours were 99% of the total, so this number may be much smaller (this study did not look at all disease stages, so this figure has not been used to derive an estimate).

The European Society for Medical Oncology (ESMO) Practice Guidelines for bladder cancer states that approximately 50% of patients with advanced or metastatic disease are ineligible for cisplatin, due predominantly to renal dysfunction, poor performance status and/or co-morbidity. Of these patients, some may be suitable to receive other systemic therapies, such as carboplatin + gemcitabine, with the remainder unsuited to any systemic therapy (as described above).

⁸ ACIM Book – Bladder Cancer. <https://www.aihw.gov.au/reports/cancer/acim-books/contents/acim-books>

⁹ <https://bladder-cancer.canceraustralia.gov.au/statistics>

¹⁰ Chen EC, McCahy P, Frydenberg M (2011) *Long term outcomes of radical cystectomy—Monash Medical Centre Experience.* Asia Pac J Clin Oncol 7(Suppl s4):117–195.

In terms of the applicability to Australian patients of the European statistics (or other regions), a 2014 review of Australian bladder cancer epidemiology¹¹ states “The incidence and mortality rates of bladder cancer in Australia closely parallel those of other developed countries”. In addition, the proportions of histological sub-types also mirror international figures.

The SBA will report what proportions of the test-eligible patients fall into the two groups of high and low PD-L1 expression (no estimated split was provided in the application). *The applicant estimated that uptake of the test could be 1415 patients per year.*

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

Patients that are test-eligible would have undergone assessment to confirm a diagnosis of stage IV urothelial cancer, either as an initial diagnosis or during surveillance for earlier stage disease recurrence/progression. Tests for this diagnostic work-up for bladder lesions could include exploratory imaging; urine cytology; cystoscopy; renal function tests; Computed Tomography (CT) or Magnetic Resonance Imaging to confirm staging; biopsy and histopathology (in new presentations) of primary tumour or metastases; chest X-ray or whole body CT for potential metastases in high risk patients, depending on symptoms such as bone pain and disease history. Cystoscopy is not relevant for tumours of the upper urinary tract (including renal pelvis and ureters) and staging requires different imaging methods.

An assessment to determine suitability for systemic treatment would also be performed as part of standard of care.

It was considered whether histological confirmation of urothelial tumour type is an additional test to differentiate from non-urothelial cancers of the bladder (similar to confirmation of non-small cell lung cancer [NSCLC] as non-squamous or ‘not otherwise specified’ for tyrosine kinase inhibitor treatment). No additional criterion is needed because the patient population is explicitly urothelial cancer and histology to inform this specific diagnosis in patients presenting with bladder cancer is part of the standard work-up.

Intervention

The proposed test is an immunohistochemistry (IHC) assay to detect PD-L1 protein as a measure of PD-L1 gene expression prior to treatment. PD-L1 testing is not a routine part of Australian clinical practice. Nevertheless, the development and marketing of PD-L1 inhibitor medicines is driving establishment of this type of test in Australian laboratories, at least for non-small cell lung cancer. A pilot programme for testing in NSCLC is underway under the aegis of the Royal College of Pathologists Australasia (RCPA) in collaboration with the United Kingdom National External Quality Assessment (NEQAS)(Application 1440 public summary document).

In response to a request for targeted consultation for this application, the RCPA “expressed [its] concerns about the imperfect nature of PD-L1 IHC as a predictive biomarker for selecting patients likely to respond to immunotherapy, but acknowledges there is no clear alternative assay or indeed gold standard for immunohistochemistry testing.”

¹¹ Cheluvappa R1, Smith DP, Cerimagic S, Patel MI. A comprehensive evaluation of bladder cancer epidemiology and outcomes in Australia. *Int Urol Nephrol.* 2014 Jul;46(7):1351-60.

The applicant proposes that all patients who are test-eligible should receive one of two immunotherapy treatments:

- durvalumab monotherapy in patients with high tumour PD-L1, or;
- combination durvalumab + tremelimumab therapy in patients with low (or no) tumour PD-L1.

The expression status is determined using a three-step scoring assessment of the IHC stained tissue (described below). The test will not be used to exclude patients from access to durvalumab based on PD-L1 expression.

The applicant confirmed that addition of tremelimumab (an inhibitor of a different immune system pathway) is *necessary* to mitigate the smaller treatment benefit likely to be observed with a PD-L1 inhibitor in patients with low or no tumour PD-L1 expression. The applicant should expand on the biological rationale for this in the SBA.

This is not a test for monitoring of patient disease or treatment response.

The applicant is also applying for the same intervention (test and drug combinations) in first line stage IV NSCLC (application 1486), which was considered at August 2017 PASC.

Health Professionals

Consistent with other genetic tests listed on the MBS this PD-L1 test will be ordered by treating a specialist (oncologist and/or urologist) and not by general practitioners.

The service would be rendered by an *anatomical* pathologist, *with the appropriate training in this test*. This test is not appropriate as a pathologist determinable service. Pathology laboratories that are both NATA (National Association of Testing Authorities) accredited and enrolled in a Quality Assurance Programme for PD-L1 testing should render the service to manage potential variability and other quality issues for this type of method.

Sample material

The specimen for testing would be tumour tissue from resection or (re-)biopsy. The proposed IHC test requires enough tumour tissue to make formalin fixed paraffin embedded (FFPE) sections for staining and scoring, so less invasive options like aspirate or needle biopsy would be inappropriate. PASC considered that cytology specimens should be excluded for application 1457.

MSAC has previously considered that PD-L1 expression is not stable during the course of disease and may be inducible (Application 1414 Public Summary Document). Thus for patients who first presented with an earlier stage of disease, re-biopsy would be required upon disease progression and archived tissue would be unsuitable as the test specimen.

It was considered whether there are any features of this disease that would preclude re-biopsy in patients. Where there is residual/recurrent tumour at the primary or nearby sites, re-biopsy would be relatively straightforward, (e.g. of the bladder using cystoscopy). However, in patients who have previously had a cystectomy and where metastases are restricted to distant sites such as the lung or liver, re-biopsy poses significant risks (e.g. of pneumothorax). *Harms due to re-biopsy should be included in the SBA.*

Test Frequency

The test frequency would be once per patient lifetime. Multiple tests per lifetime would be an issue only for disease monitoring or if PD-L1 inhibitors became available for earlier stages of disease.

Test Platform

The clinical trial assay used for PD-L1 testing has been commercialised as the Roche/Ventana SP263 PD-L1 IHC kit. This kit uses a SP263 anti-PD-L1 rabbit monoclonal antibody.

Paragraph Redacted

The manufacturer's website states that the kit has a CE Mark in the European Union and it is approved as a complementary diagnostic in the United States¹². A complementary diagnostic is one that FDA considers to be informative but not mandatory for treatment (c.f. companion diagnostic).

Three other monoclonal antibodies have been used to develop commercial anti-PD-L1 IHC tests: Ventana rabbit SP142; Dako rabbit 28-8; Dako mouse 22C3. Results obtained with each of these and SP1263 (largely in NSCLC) have been observed to be highly variable and have been the subject of a number of concordance studies.

The applicant plans to present a concordance study that compares Ventana SP263, Dako 22C3 and Dako SP142 tests using 500 archived urothelial cancer tissue specimens in the SBA.

Scoring of Tests

The assay is used to determine the percentage of cells staining for PD-L1 expression, measured as a total proportion score. Tumours will be scored using a three-step assessment as either high or low PD-L1 expression. Patients in the DANUBE pivotal trial have been stratified prior to randomisation according to high or low expression. Scoring counts the cells that show PD-L1 membrane staining of any intensity in tumour cells, and staining of any intensity in infiltrating immune cells. USA product information states "The cellular staining pattern for VENTANA PD-L1 (SP263) Assay is membranous and/or cytoplasmic staining of tumor cells. Immune cells demonstrate linear membrane, diffuse cytoplasmic, and/or punctate staining." Thus, scoring does not include all PD-L1 staining that may be observed. Cytoplasmic staining in tumour cells is not scored, but scoring of immune cells can include membrane and cytoplasmic staining. This is different to Application 1505 which involves staining of tumour cells only.

In the sponsor's earlier clinical trials, tumour score was defined as:

- High PD-L1 expression: tumour cells \geq 25% or immune cells \geq 25%;
- Low PD-L1 expression: tumour cells $<$ 25% or immune cells $<$ 25%

In the phase III clinical trial, an additional criterion was added (to take account of exceptional cases observed in earlier trials) where the number of immune cells is only 1% of the tumour sample.

Consequently, the Phase III (DANUBE) trial criteria for high PD-L1 status is *a three-step assessment to determine* if the patient's tumour specimen meets any of the following criteria:

1. \geq 25% of tumour cells exhibit membrane staining; OR,
2. In specimens where the immune cells present is greater than 1%: 25% of immune cells (or greater) exhibit positive staining, OR;

¹² <http://www.ventana.com/roche-receives-fda-approval-complementary-pd-l1-sp263-biomarker-test-urothelial-carcinoma/>

3. In specimens where the immune cells present is only 1%: all immune cells present show positive staining.

All other tumours are defined as low PD-L1 expression, including no PD-L1 expression.

Scoring *was confirmed by the applicant* to be the same between the DANUBE trial, the US test kit approval¹³ and the proposed scoring for an MBS item, and it is assumed that this scoring method will be reflected in the TGA application for the test kit. *Although patients in the DANUBE trial have been stratified according to PD-L1 status, their tumour expression levels have not been used to guide treatment selection. Hence the trial results should facilitate a comparison of the two PD-L1 expression states versus the two treatment options.*

Of note: low PD-L1 expression includes absence of any PD-L1 expression. Clinical trial data and the requested PBS listing for the combination therapy will include 'no expression' patients. [This touches upon an issue explored in previous PD-L1 applications 1414 and 1440, in which MSAC considered that patients defined by those tests as 'test-negative' may benefit from immunotherapy treatment, but just not as much as the benefit observed in those defined as 'test-positive'.]

It would be informative if the SBA presents 'no PD-L1' patients as a sub-group of the low PD-L1 patients to understand whether the absence of the biomarker (by this test) shows any trend to a different or lower response.

The RCPA provided feedback on PD-L1 scoring proposed in this application:

"[T]he scoring cut-offs used to define a positive result in the current application (>25% tumour or immune cell staining) differ from those in Application 1457 (pembrolizumab in bladder cancer, >10% combined score), which are both different from the scoring applied to lung cancer in several applications for PD-L1 testing currently in progress, adding to the difficulty for pathologists trying to assess a case. Issues with inter-operability of assays and testing platforms are still awaiting resolution.

MSAC has noted the difficulties posed by multiple PD-L1 tests, antibodies and scoring methodologies (applications 1414; 1440). Concordance studies can only address a subset of these technical issues.

Treatment consequent on test results

Once patients' tumours are classified as low PD-L1 or high PD-L1, the applicant proposes the following treatment options:

- High expression patients would be eligible to receive durvalumab monotherapy (1.5 g IV q4w for up to a year) and
- Low/no expression patients would receive combination tremelimumab (75 mg IV q4w for up to 4 cycles) + durvalumab (1.5 g IV q4w).

All the PD-L1 applications recently considered by the Committees have proposed a numerical threshold as a definition of test positivity. Each application and therapeutic indication has featured a different PD-L1 expression threshold and scoring method. According to this proposal, scoring of sections after IHC staining would include both tumour cells as well as infiltrating immune cells showing PD-L1 staining in urothelial tumour samples.

¹³ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=394004>

The rationale for the chosen threshold between low and high PD-L1 should be described in the SBA. For example: are there any other characteristics observed at the threshold that would support the biological plausibility of this value; does expression change for other PD-1 pathway markers? *The PASC noted that a different threshold may result in different clinical utilities for the offered treatment options.*

Healthcare Setting

This test requires fresh tissue from resection or biopsy. A biopsy of advanced urothelial cancer is not a procedure that can be performed in a specialist's suite. A biopsy would require a hospital inpatient admission or surgical day-stay (as an outpatient) and the tissue sent to the hospital laboratory. It is unlikely that this test would be rendered in a private pathology laboratory in the community although this assumption would benefit from specialist input. In terms of whether the MBS rebate would be 75% or 85%, all tissue samples for testing are assumed to be obtained in a hospital setting, in which case a 75% rebate applies if the service is MBS-eligible.

Pathology services in the public hospital system are not MBS-eligible, including those for outpatient units (unlike diagnostic imaging) – the cost of pathology tests in public hospital laboratories is borne by the States and Territories. The only exception is if the patient opts to be a private patient in a public hospital (e.g. so they can be treated by the specialist who treats them outside the hospital). As such, only PD-L1 test utilisation rendered for private patients, or in private hospitals, would be MBS-eligible.

The SBA should consider the proportions of private hospitals versus public hospitals where the PD-L1 tests would be performed to inform utilisation and financial impact estimates.

Comparator

The primary comparator is no PD-L1 testing and current standard of care which is platinum-based chemotherapy (cisplatin + gemcitabine or carboplatin + gemcitabine, depending on the patient's suitability to receive cisplatin).

In order to demonstrate the clinical utility of the test, the applicant also plans to present a comparison of the efficacy and safety of durvalumab and durvalumab + tremelimumab treatment with PD-L1 testing versus without PD-L1 testing.

Comparator for the test

The comparator for the PD-L1 test is 'no testing'. There is no reference standard for PD-L1 testing in Australia. The evidentiary standard is the assay as implemented in the clinical trials. *The applicant has confirmed that this assay is the same as the commercially available kit.* The SBA should report whether the trial employed the test at a central laboratory or if any local testing was performed.

Other PD-L1 co-dependent tests recently considered by the MSAC have only enrolled test-positive patients in the pivotal clinical trials. However, this application proposes to give durvalumab monotherapy to high PD-L1 expression patients and durvalumab + tremelimumab to those with low or no PD-L1 tumour expression. The patients in the DANUBE trial are being stratified (prior to randomisation) according to low versus high PD-L1 expression using the Roche/Ventana assay.

The PASC noted that other assays relevant for a comparison of analytical performance would include the Agilent Technologies Pty Ltd/DAKO PD-L1 PharmDx assay and any alternative PD-L1 expression methods in urothelial cancer.

Comparator for the medicines

The comparators for both durvalumab monotherapy and durvalumab + tremelimumab combination therapy will be either cisplatin + gemcitabine or carboplatin + gemcitabine, depending on the patient’s suitability to receive cisplatin. The DANUBE trial patients have been stratified according to their eligibility to receive cisplatin. Carboplatin is a recommended alternative for those patients unsuitable to receive cisplatin due to factors such as poor renal function, poor performance status and others. This is the standard of care for patients with locally advanced or metastatic urothelial cancer, as described in a 2011 Cochrane review¹⁴ that concluded “gemcitabine plus cisplatin may be considered the first choice for treatment of metastatic bladder cancer. [...] Patients unable to tolerate cisplatin may benefit from gemcitabine plus carboplatin.” Both options are preferable in terms of safety to MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) which was standard of care prior to availability of gemcitabine.

Patients with non-muscle invasive disease are unlikely to be included in a population limited to stage IV disease, thus comparators for this type of urothelial cancer have not been considered.

Comparing the co-dependent elements

As with other co-dependent tests/drug combinations, four comparisons are relevant:

	Test intervention	Test comparator
Drug intervention	PD-L1 test + either durvalumab or durvalumab + tremelimumab	No test + either durvalumab or durvalumab + tremelimumab
Drug comparator	PD-L1 test+ platinum-based chemotherapy	No test + platinum-based chemotherapy

The DANUBE trial will compare the two scenarios in the left hand column. Existing published data is available regarding efficacy of the two comparator regimens that comprise the current standard of care, noting that the carboplatin + gemcitabine is marginally inferior to cisplatin + gemcitabine in terms of median survival. As is usually the case with co-dependent clinical data packages, there will be no true assessment of ‘no testing’. However, none of the patients will be excluded from the DANUBE trial based on PD-L1 status, so some of this comparison can be inferred. , though we will not know how effective monotherapy of either drug would be in an untested population, nor effectiveness of the combination therapy in high PD-L1 patients.

Secondary comparators

PASC confirmed pembrolizumab in first line PD-L1 positive urothelial cancer is a near comparator in the event that the interventions in application 1457 are listed. This comparison is only relevant for DANUBE patients that have high PD-L1 expression. The SBA will need to consider the transitivity of

¹⁴ Shelley M, Cleves A, Wilt TJ, Mason M. *Gemcitabine for unresectable, locally advanced or metastatic bladder cancer*. Cochrane Database of Systematic Reviews 2011, Issue 4. Art. No.: CD008976.

the patient groups in this comparison, given pembrolizumab is only proposed in those ineligible for cisplatin, whereas durvalumab is proposed for those ineligible and eligible for cisplatin.

Outcomes

The PASC considered the following outcomes would be relevant for the SBA.

Safety

Adverse events associated with biopsy and re-biopsy; re-biopsy rates

Negative consequences of false 'low' PD-L1 expression results and false 'high' PD-L1 expression results

Health-related

Overall survival

Disease-specific survival

Progression-free survival

Time to progression

Rate of recurrence

Overall response rate

Duration of response

Quality of life

Test Outcomes

Trial-based (evidentiary standard) PD-L1 IHC assay analytical performance

Comparative analytical performance across PD-L1 IHC assay options likely to be available in Australia

Re-testing rates (test failure)

Clinical validity (comparing the prognosis over time of patients with 'low' PD-L1 expression results and patients with 'high' PD-L1 expression results)

Clinical utility (comparing the extent of incremental treatment effect over prognosis of the proposed treatment regimens with and without prior PD-L1 expression testing)

Cost-effectiveness

Incremental cost per life year gained

Incremental cost per quality of life year (QALY) gained

Healthcare resources

Cost of testing per patient tested

Cost of treatment per patient with a 'low' PD-L1 expression result

Cost of treatment per patient with a 'high' PD-L1 expression result

Test turn-around time

Estimated number of patients being tested

Net overall healthcare costs

Net cost to the MBS

In addition, during preparation of the draft PICO prior to PASC it was considered the following may be relevant:

- Any in-trial evaluation of test performance such as sample exchange between sites, central versus local laboratory testing; comparison with reference sample tissues. Parameters relevant to Clinical Effectiveness (Specificity; Positive predictive value; Negative predictive value; Receiver operator characteristic (ROC)) will only come from a comparison of the trial assay against other, different PD-L1 assays and will not come from the trial data alone.
- The Comparative Performance of PD-L1 Testing Methods should however consider the parameters Specificity; Positive predictive value; Negative predictive value; Receiver operator

characteristic (ROC) for the other available PD-L1 platforms/antibodies in Australia, or at least those where a 25% expression threshold is used for scoring.

- The proportion of test-eligible patients unsuitable for biopsy or re-biopsy;
- The number needed to test to observe an incremental benefit in low PD-L1 patients; in high PD-L1 patients;
- Inter-operator variability (intermediate precision) observed for the trial-based assay; and if possible, comment on likely achievable performance in Australian laboratories compared with DANUBE central reference laboratory
- In terms of negative consequences for patients that are mis-classified (false results):
 - Consider a patient whose result is false high PD-L1 and receives monotherapy when they are in fact low PD-L1 and should be receiving combination therapy. If the additional agent is necessary for low PD-L1 patients, this suggests that monotherapy is likely to be ineffective or less effective than platinum therapy in these patients.
 - In the reverse situation (high PD-L1 patient receives false low PD-L1 result), is the combination therapy associated with poorer safety than monotherapy?
- ORR is assumed to include what (if any) proportion of responses were complete responses.
- Drug safety should be presented for monotherapy and combination therapy, or identifying where the two differ.
- Discontinuations due to toxicity; toxicity leading to hospitalisations, dose reduction or dose modification.
- The tolerability of standard of care is a concern in this population – if the proposed therapies are associated with high toxicity and discontinuations, it may not follow that these biologics will replace platinum therapy. If the trial data indicate a high rate of discontinuations, the SBA should describe whether there are any common characteristics in the discontinuing patients that makes them identifiable prior to commencement. Will these patients receive platinum-based therapy after a trial of durvalumab-containing therapy?
- If possible, patient relevant outcomes specific to this disease (e.g. cystectomies avoided)

Healthcare system

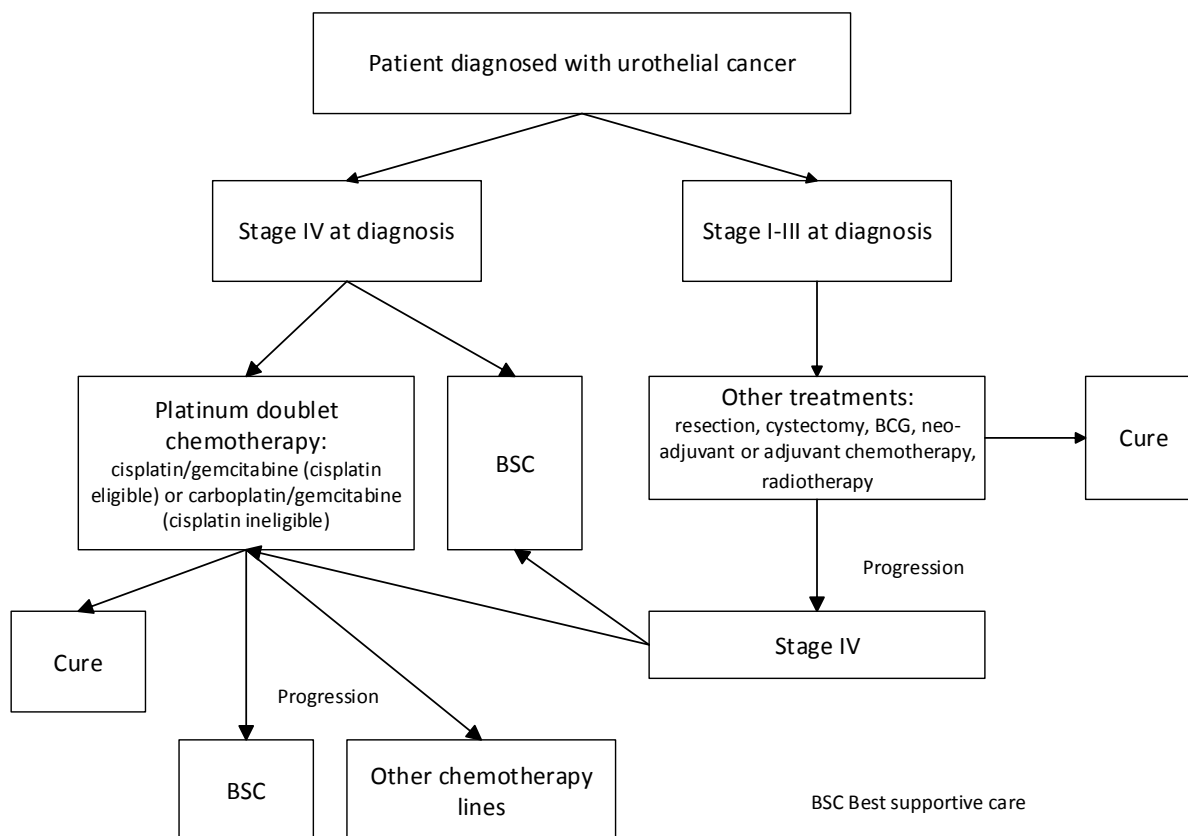
There is unlikely to be a change in the number of specialist consultations required in these first stages of diagnosis and evaluation of treatment options.

Testing will require a fresh biopsy and hospital admission (as a day patient) for imaging and surgery. A biopsy would require a general anaesthetic if it involved a cystoscopy, but others may be performed with a local anaesthesia. Overnight admission would be unlikely except in the event of morbid complications. The adverse event data from the clinical trials should inform a comment on the likelihood and type of admissions/extension of hospitalisation due to complications from biopsy.

Both proposed and comparator drugs are infusions, thus there will be no change to the treatment setting for administration of these, though frequency of each will be different.

Current clinical management algorithm for identified population

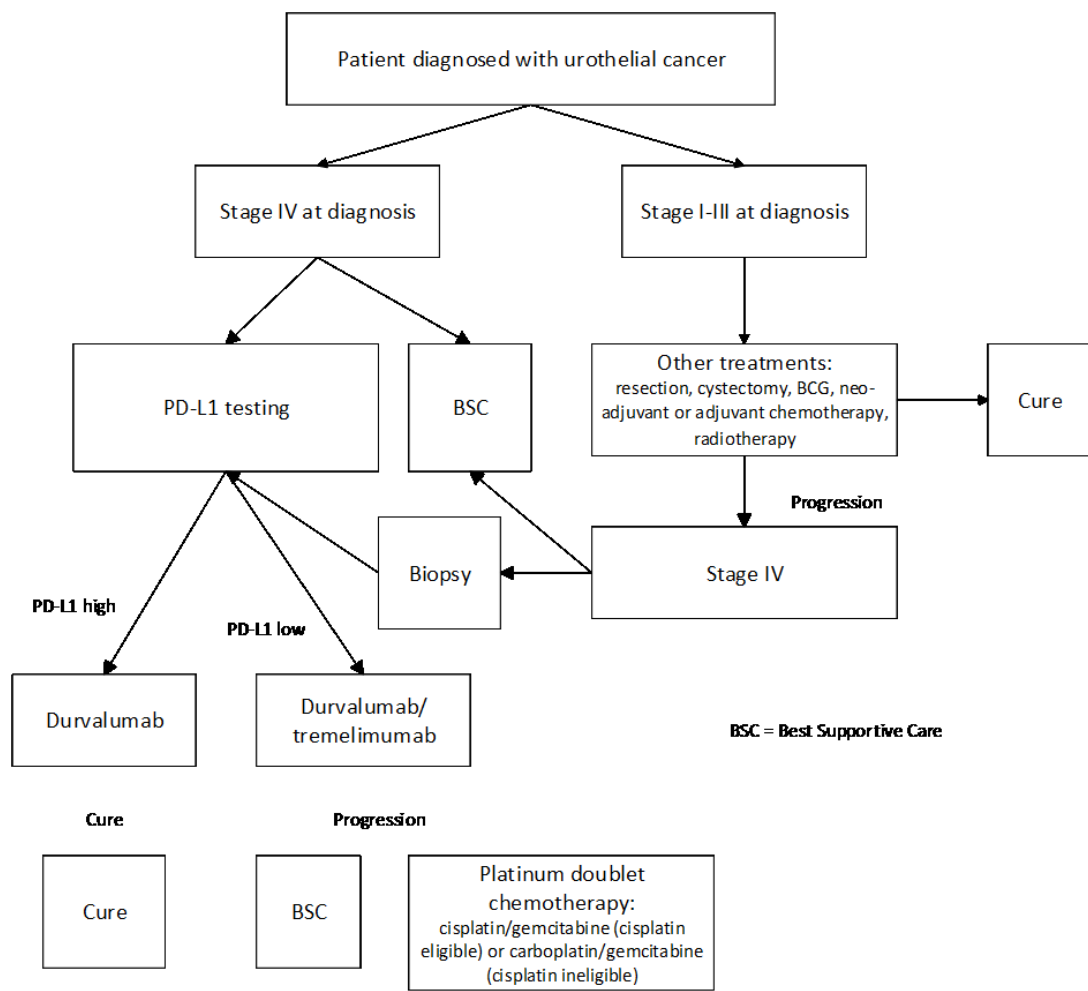
The applicant describes the current treatment algorithm for these patients as follows:



A biopsy step is assumed to be part of the box ‘Patient diagnosed with urothelial cancer’ as this is part of the diagnostic work-up for standard of care. It may not be useful to break this algorithm down to that level of detail given the other assessments that would necessarily be included at that step. A cure is highly unlikely following platinum-based therapy in stage IV disease, especially in patients with distant metastases. Other stage IV patients would require post-chemotherapy cystectomy/metastectomy for a cure to be possible. This algorithm should reflect in both the stage IV boxes exclusion of patients who are unsuited to systemic therapy, and those who would be candidates for resection.

Proposed clinical management algorithm for identified population

The applicant describes the future treatment algorithm including the proposed treatments as follows:



The step 'Biopsy' after progression to stage IV from earlier disease should be 'Re-biopsy'. A biopsy step is assumed to be part of the box 'Patient diagnosed with urothelial cancer' as this is part of the diagnostic work-up for standard of care. As noted above, the stage IV boxes should reflect exclusion of patients who are unsuited to systemic therapy, and those who would be candidates for resection.

Proposed economic evaluation

The applicant proposes that PD-L1 testing and treatment with the following is superior to no PD-L1 testing and standard of care in all patients:

- PD-L1 test + durvalumab monotherapy versus no test + standard of care in patients with high PD-L1 expression, and;
- PD-L1 test + durvalumab + tremelimumab combination therapy versus no test + standard of care in patients with low PD-L1 expression

If this claim is supported by the clinical evidence presented in the application, a cost-utility analysis would be the most appropriate type of economic evaluation to present.

The applicant has also proposed pembrolizumab in first line PD-L1 positive urothelial cancer as a potential secondary comparator in the event that the interventions in application 1457 are listed. The applicant will present a claim that the combination therapy would be non-inferior to pembrolizumab in PD-L1 high patients. If this claim is supported by the evidence, then a cost-minimisation analysis would be appropriate.

Proposed item descriptor

The applicant proposed the following descriptor:

Category 6 – Pathology Services
MBS item number
Proposed item descriptor: Immunohistochemical examination of biopsy material (tumour cells and immune cells) from a patient diagnosed with unresectable Stage IV urothelial cancer using a programmed cell death ligand 1 (PD-L1) antibody to determine if the requirements relating to PD-L1 status for access to durvalumab or durvalumab/tremelimumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.
Fee: To be determined Benefit: To be determined

A review of similar test items was undertaken to inform comments on the item descriptor.

MBS Category and Group

This would be an item under Category 6 Pathology Services; within that category, this test would fall into Group P7 Genetics. This is the same as all other items for co-dependent genetic tests required for access to PBS medicines.

Similar Items

There are no IHC co-dependent tests currently listed on the MBS. The co-dependent tests for in situ hybridisation of tumour biomarkers ALK (73341) and Her-2 (73342) rely on prior IHC testing as a triage test (the IHC method is otherwise associated with a high rate of false positives). IHC items are listed on the MBS for more general purposes (not co-dependent).

Looking at other, existing MBS co-dependent pathology items (in P7 Genetics):

- Each item covers testing for one or more PBS medicines in a single therapeutic indication, though the population may not be identical for each medicine.
- The existing item descriptors specify tumour type and disease stage, the target biomarker, the relevant PBS medicines, whether specialists or GPs will order the test, and test frequency.
- The MBS descriptors do not state the line of therapy, test scoring criteria, nor (typically) histology, nor qualifiers such as 'unresectable' (with the exception of BRAF for vemurafenib/dabrafenib). Each of these would however be specified in the corresponding PBS restrictions for drug access.

Of the PD-L1 testing applications considered by the Committees so far, none have been recommended as yet. The applicant has suggested, if Application 1457 was recommended and an item for PD-L1 testing listed on the MBS, that item would be a basis for amendment. The populations are somewhat different and an item would need to accommodate both:

- 1457: locally advanced or metastatic; silent on (un)resectable disease status; cisplatin ineligible only, PD-L1 high;
- 1506: stage IV (metastatic only); unresectable only; must be eligible for systemic therapy (either cisplatin or carboplatin), PD-L1 all-comers (high PD-L1, low PD-L1 including no expression)

However, most of these criteria need not appear in the descriptor wording (and could instead be matters for the PBS restrictions). The key differences would be disease stage, test platform and scoring. At the request of the Department, wording for corresponding PBS restrictions has been mocked up (Appendix 1) that reflect the criteria discussed in this PICO Confirmation.

Fee

The actual cost of IHC methods vary depending on the cost of the antibody, tests rendered using a commercial kit or platform may cost more, though this is a choice for the pathologist. The MBS fee for IHC testing of breast cancer tissue for the three standard tumour biomarkers including Her-2 is \$74.50 (Group P6 Tissue Pathology item 72848). *PASC considered this a benchmark in terms of complexity given that PD-L1 will require scoring of more than one cell type.* All other IHC tests of biopsy material are rendered under the MBS general items for IHC (72846, 72847, 72849, 72850) (fees of \$59.60 - \$119.20).

Descriptor

Based on the above, the alternative descriptor below was considered by PASC.

Category 6 PATHOLOGY SERVICES – Group P7 Genetics
<p><u>[Item number]</u></p> <p><u>Immunohistochemistry (IHC) test of tumour tissue from a patient with stage IV urothelial cancer requested by a specialist or consultant physician to determine if requirements relating to PD-L1 expression status for access to durvalumab (including durvalumab in combination with tremelimumab) under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Tumour tissue for testing must be obtained at the time of stage IV diagnosis.</u></p> <p><u>Maximum of one test per patient lifetime.</u></p> <p><u>Fee: \$TBD</u></p> <p><u>Note:</u> <u>Tumour tissue is defined as high PD-L1 expression if any of the following apply:</u></p> <ul style="list-style-type: none">• 25% (or greater) PD-L1 positive tumour cells, OR;• In specimens where the immune cells present is greater than 1%: 25% (or greater) PD-L1 positive immune cells, OR;• In specimens where the immune cells present is only 1%: all immune cells present are PD-L1 positive. <p><u>Tumour specimens meeting none of the above three criteria are defined as low PD-L1 expression, including those with no PD-L1 expression.</u></p>

PASC considered that scoring criteria in the alternative proposal should be included in a note as they are particularly complex for this test proposal. The PASC noted that in the event a sample is inadequate, a patient would not be billed so the limit of one test per lifetime is appropriate. Final wording would depend on the results of the DANUBE trial which may affect patient eligibility.

PASC considered that scoring (and test platform) for different types of PD-L1 tests would make it essential for the specialist ordering the test to specify the drug(s) being considered for the pathologist to be able to render the correct test. This could potentially be included in a note. Pathologists would need training on the different tests, including scoring.

PASC supported the descriptor text below, based on consistency with other PD-L1 items more advanced in the MSAC process.

Category 6 – Pathology Service

Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the programmed cell death ligand 1 (PD-L1) antibody of biopsy material (tumour cells and immune cells) from a patient diagnosed with unresectable Stage IV urothelial cancer to determine if requirements relating to PD-L1 expression status for access to durvalumab or durvalumab/tremelimumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Maximum of one test per patient lifetime.

MBS fee: \$74.50

Chemotherapy Items for [Public][Private] Hospital Use

DURVALUMAB

Authority Required

Stage IV urothelial cancer

Treatment Phase: TBD

Clinical criteria:

The treatment must be as monotherapy,

AND

The condition must be unresectable,

Population criteria:

Patient must not have received prior chemotherapy for this condition,

AND

Treatment must not be in a patient unsuitable to receive systemic anticancer therapy.

AND

Patient must have evidence of high PD-L1 expression in tumour material obtained at the time of stage IV diagnosis by immunohistochemistry (IHC) testing, defined as any of:

- 25% (or greater) positive tumour cells, OR;
- In specimens where the immune cells present is greater than 1%: 25% (or greater) positive immune cells, OR;
- In specimens where the immune cells present is only 1%: all immune cells present are positive.

Patients not meeting at least one of the above criteria are defined as low PD-L1 expression.

Chemotherapy Items for [Public][Private] Hospital Use

DURVALUMAB + TREMELIMUMAB

Authority Required

Stage IV urothelial cancer

Treatment Phase: TBD

Clinical criteria:

The condition must be unresectable,

Population criteria:

Patient must not have received prior chemotherapy for this condition,

AND

Treatment must not be in a patient unsuitable to receive systemic anticancer therapy.

AND

Patient must have evidence of low PD-L1 expression in tumour material obtained at the time of stage IV diagnosis by immunohistochemistry (IHC) testing, defined as any of:

- Less than 25% positive tumour cells, OR;
- In specimens where the immune cells present is greater than 1%: less than 25% positive immune cells, OR;
- In specimens where the immune cells present is only 1%: anything less than 100% positive immune cells, OR;
- Absence of any PD-L1 positive cells.