Australian Government

Department of Health

Application Form

(New and Amended Requests for Public Funding)

(Version 2.5)

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires in order to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

The application form will be disseminated to professional bodies / organisations and consumer organisations that have will be identified in Part 5, and any additional groups that the Department deem should be consulted with. The application form, with relevant material can be redacted if requested by the Applicant.

Should you require any further assistance, departmental staff are available through the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Phone: +61 2 6289 7550
Fax: +61 2 6289 5540
Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):N/A
Corporation name: AstraZeneca Pty Limited
ABN: **Redacted**
Business trading name: **Redacted**

Primary contact name: Redacted

Primary contact numbers
Business: **Redacted**
Mobile: **Redacted**
Email: **Redacted**

Alternative contact name: Redacted

Alternative contact numbers
Business: **Redacted**
Mobile: **Redacted**
Email: **Redacted**

2. (a) Are you a consultant acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, what is the Applicant(s) name that you are acting on behalf of?

Insert relevant Applicant(s) name here.

3. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

☐ Yes ☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

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.

5. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

In Australia in 2013, bladder cancer was the eighth most commonly diagnosed cancer in men (age-standardised rate 16.5 cases per 100,000) but was much less common in women (age-standardised rate 4.1 cases per 100,000).[1] The 5-year relative survival for bladder cancer patients has slowly declined from 1984-2013.[1]

Bladder cancer is rare under the age of 50 and usually presents in old age. Risk factors for bladder cancer include cigarette smoking, carcinogenic chemical exposure, genetic predisposition and prior radiotherapy/chemoradiation in the pelvis/lower abdomen. More than 90% of bladder cancers form in the lining of the urinary tract (the urothelium) and are known as urothelial carcinomas, or transitional cell carcinomas.[2,3] Urothelial cancers most commonly occur in the bladder, but may also be found in the renal pelvis, ureters and urethra.

Bladder cancer is a highly immunogenic tumour type,[4] consequently immunotherapy treatments for bladder cancer may alter the disease process. This Application proposes durvalumab or durvalumab/tremelimumab as first line treatment for patients with unresectable Stage IV transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder and urethra).

[1] Australian Institute of Health and Welfare (AIHW) Cancer in Australia 2017, p.82-83

[2] Bladder cancer – transitional cell carcinoma Fact Sheet Urological Society of Australia and New Zealand (http://www.usanz.org.au/uploads/65337/ufiles/bladder-cancer.pdf)

[3] Cancer Australia Bladder Cancer https://canceraustralia.gov.au/affected-cancer/cancer-types/bladder-cancer

[4] Schumacher T and Schrieber R. Science 3 April 2015

6. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

PD-L1 is expressed on the surface of tumour cells and immune cells in a broad range of cancer types, including urothelial cancer. PD-L1 aids cancers in evading detection and elimination by the immune system by supressing the anti-tumour T-cell response. The level of PD-L1 expression can be assessed using immunohistochemical (IHC) testing with antibodies that bind specifically to the PD-L1 expressed on the surface of tumour cells or immune cells.

Durvalumab (MEDI4736) is a human monoclonal antibody that inhibits binding of PD-L1 to programmed cell death receptor 1 (PD-1). Tremelimumab (MEDI1123) is a human monoclonal antibody which specifically binds to cytotoxic T-lymphocyte antigen -4 (CTLA-4), prolonging T cell activation and proliferation and enhancing T-cell anti-tumour activity.

This application is a **co-dependent** request for MBS listing of PD-L1 testing to determine which Stage IV unresectable urothelial cancer patients have a high level of PD-L1 expression (defined as tumour cells ≥ 25% or immune cells ≥ 25%)* in order to qualify for requested PBS access to 1st line durvalumab monotherapy treatment, and which Stage IV unresectable urothelial cancer patients have a low level of PD-L1 gene expression (defined as tumour cells < 25% or immune cells < 25%)* in order to qualify for requested PBS access to 1st line durvalumab/tremelimumab combination treatment.

*When the immune cell area represents ≤1% of the total tumour area PD-L1 expression is defined as high when baseline tumour expression was tumour cells ≥ 25% and/or immune cells = 100% and PD-L1 low/negative when baseline tumour expression was tumour cells < 25% and immune cells <100%.

7. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

There are a number of MBS items for immunohistochemical (IHC) testing however none of these current items is specific for PD-L1 testing of patients with urothelial cancer to determine PBS access to PD-L1/PD-1 blockers. At the time of this application the medical service would still require a new MBS item number, however should MSAC PICO Confirmation 1457 lead to a new MBS item number for PD-L1 testing for access to pembrolizumab in metastatic urothelial cancer patients, then the requested medical service may require an amendment to this MBS listing to include access to durvalumab or durvalumab/tremelimumab.

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Not currently applicable.

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

i. ☐ An amendment to the way the service is clinically delivered under the existing item(s)
ii. ☐ An amendment to the patient population under the existing item(s)
iii. ☐ An amendment to the schedule fee of the existing item(s)
iv. ☐ An amendment to the time and complexity of an existing item(s)
v. ☐ Access to an existing item(s) by a different health practitioner group
vi. ☐ Minor amendments to the item descriptor that does not affect how the service is delivered
vii. ☐ An amendment to an existing specific single consultation item
viii. ☐ An amendment to an existing global consultation item(s)
ix. ☐ Other (please describe below):

Insert description of 'other' amendment here

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

No other source of funding for PD-L1 testing other than the MBS is sought, however in this co-dependent submission public funding for PBS access to durvalumab or durvalumab/tremelimumab is being sought.

(g) If yes, please advise:

Insert description of other public funding mechanism here

8. What is the type of service:

☐ Therapeutic medical service
☐ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☒ Co-dependent technology
☐ Hybrid health technology

9. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☐ To be used as a screening tool in asymptomatic populations
ii. ☐ Assists in establishing a diagnosis in symptomatic patients
iii. ☐ Provides information about prognosis
iv. ☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions
vi. ☐ Is for genetic testing for heritable mutations in clinically affected individuals and, when also appropriate, in family members of those individuals who test positive for one or more relevant mutations (and thus for which the Clinical Utility Card proforma might apply)

10. Does your service rely on another medical product to achieve or to enhance its intended effect?

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☒ No

(b) If yes, please list the relevant PBS item code(s):

Insert PBS item code(s) here: Not applicable

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☒ No

An integrated co-dependent submission to MSAC/PBAC is proposed for PD-L1 testing to determine PBS access to durvalumab or durvalumab/tremelimumab as first line treatment in patients with unresectable Stage IV urothelial cancer.

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: The tradename has yet to be determined for durvalumab (also known as MEDI4736).
The tradename for tremelimumab (also known as MEDI1123) has yet to be determined.
Generic names: durvalumab; tremelimumab

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List? Not applicable

☐ Yes
☐ No

(b) If yes, please provide the following information (where relevant): Not applicable

Billing code(s): Insert billing code(s) here
Trade name of prostheses: Insert trade name here
Clinical name of prostheses: Insert clinical name here
Other device components delivered as part of the service: Insert description of device components here

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)? Not applicable

☐ Yes
☐ No

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to? Not applicable

☐ Yes
☐ No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s): Not applicable

Insert sponsor and/or manufacturer name(s) here

13. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: Commercially available PD-L1 test kits are single use items.
Multi-use consumables: Instrumentation/software, such as the Ventana BenchMark ULTRA IHC automated slide stainer are multi-use consumables.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: Pharmaceutical products – PD-L1 blocker durvalumab (MEDI 4736); CTLA-4 blocker tremelimumab (MEDI1123)
Manufacturer's name: AstraZeneca Pty Ltd
Sponsor's name: AstraZeneca Pty Ltd

Type of therapeutic good: In-vitro diagnostic test: Roche/Ventana SP263 PD-L1 IHC assay
Manufacturer's name: Roche Diagnostics Pty Limited
Sponsor's name: Roche Diagnostics Pty Limited

A comparison to alternative commercial PD-L1 test kits and other PD-L1 test methods for urothelial cancer will be conducted as part of a submission based on this application.

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☒ Class III
☐ AIMD
☐ N/A
The PD-L1 IVD test required to determine PD-L1 status and eligibility for PBS durvalumab or durvalumab/tremelimumab for urothelial cancer patients would be classified as a Class 3 IVD.

15. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☐ Yes (if yes, please provide details below)
☒ No

ARTG listing, registration or inclusion number: Insert ARTG number here
TGA approved indication(s), if applicable: Insert approved indication(s) here
TGA approved purpose(s), if applicable: Insert approved purpose(s) here

16. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

☐ Yes (please provide details below)
☒ No

Date of submission to TGA: Insert date of submission here
Estimated date by which TGA approval can be expected: Insert estimated date here
TGA Application ID: Insert TGA Application ID here
TGA approved indication(s), if applicable: If applicable, insert description of TGA approved indication(s) here
TGA approved purpose(s), if applicable: If applicable, insert description of TGA approved purpose(s) here

17. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

☒ Yes (please provide details below)

☐ No

Redacted

Estimated date of submission to TGA: **Redacted**

Proposed indication(s), if applicable: 1st line unresectable Stage IV urothelial cancer

Proposed purpose(s), if applicable: PD-L1 testing to determine PBS access to durvalumab monotherapy or durvalumab/tremelimumab combination therapy

PART 4 – SUMMARY OF EVIDENCE

18. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*****
1.	Phase I dose finding/Phase II dose expansion trial of durvalumab in multiple solid tumour types including urothelial bladder cancer.	Study 1108	Safety and efficacy of durvalumab in the Phase II dose expansion cohort of 191 patients with urothelial cancer. Patients were treated with durvalumab 10 mg/kg q2w for up to one year. PD-L1 expression was determined at baseline (PD-L1 high cut-off ≥25% tumour cells or immune cells; PD-L1 low <25% tumour cells or immune cells) using SP263 assay optimised for use on the BenchMark ULTRA platform [Ventana Medical Systems Inc.]. The primary endpoint was safety and tolerability; secondary endpoints included objective response rate (ORR) and overall survival (OS).	www.clinicaltrials.gov NCT01693562 http://ascopubs.org/doi/pdf/10.1200/JCO.2016.67.9761 Massard C, Gordon MS *et al* Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 Immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. *J. Clin. Oncol.* 2016 Sep 10;34(26):3119-25. http://abstracts.asco.org/199/AbstView_199_189860.html Hahn NM, Powles T, Massard C. *et al.* Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma (UC). ASCO 2017 Annual Meeting Abstract 4525.	2016/2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
	PD-L1 Assay Development and Validation in Urothelial Cancer	PD-L1 Diagnostic Assay for Urothelial Cancer	This poster describes the development and validation of an immunohistochemical PD-L1 diagnostic assay for treatment with durvalumab in urothelial cancer patients	Zajac M, Boothman AM, et al. An immunohistochemical PD-L1 diagnostic assay for treatment with durvalumab in urothelial cancer patients. European Society of Medical Oncology (ESMO) Symposium on Immuno-oncology, Lausanne, Switzerland 4-6 November 2016 Poster 26P (PDF can be supplied on request)	2016

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

**** If the publication is a follow-up to an initial publication, please advise.*

19. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.	A Phase III, randomised, open-label, controlled, multi-centre, global study of first line MEDI4736 monotherapy and MEDI4736 in combination with tremelimumab versus standard of care chemotherapy in patients with unresectable Stage IV urothelial cancer	DANUBE	Approximately 335 patients will be randomised to each of the three treatment arms; MEDI4736 monotherapy (1.5 g IV q4w), MEDI4736 (1.5 g IV q4w) in combination with tremelimumab (75 mg IV q4w for up to 4 cycles) followed by MEDI4736 (1.5 g IV q4w), and standard of care (cisplatin/gemcitabine or carboplatin/gemcitabine) as first line therapy in patients with unresectable Stage IV transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder and urethra). Patients will be stratified according to cisplatin eligibility (eligible or ineligible), PD-L1 status (low or high depending on Ventana SP263 IHC Assay) and presence or absence of visceral metastases.	www.clinicaltrials.gov NCT02516241	2018

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

****Date of when results will be made available (to the best of your knowledge).*

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

20. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

The group of health professionals who provide the medical service (PD-L1 testing) are the Royal College of Pathologists of Australasia (RCPA). A statement from the RCPA on the clinical relevance of the test is provided as an attachment to this Application.

21. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

Not applicable, the comparator for PD-L1 testing is no PD-L1 testing.

22. List the relevant consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

The consumers for PD-L1 testing and treatment with durvalumab or durvalumab/tremelimumab are patients with unresectable Stage IV urothelial cancer. The main consumer organisation representing these patients is Rare Cancers Australia (RCA). A letter from RCA supporting this application is provided as an attachment to this Application.

23. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

There are alternative products to the Roche Diagnostics PD-L1 assay available for PD-L1 testing in Australia.

Two Class 3 in-vitro diagnostic devices GMDN CT1056 Immunohistology cell marker IVD were registered in Australia in November 2016 by Agilent Technologies Australia Pty Limited (ARTG 282595 17/11/16 and ARTG 282596 17/11/16) with manufacturer DAKO.

It is also possible that pathology laboratories within the larger cancer hospitals or medical research institutes may develop in-house PD-L1 testing methods during 2017.

There is no "gold standard" PD-L1 assay established at present. A comparison of the evidentiary standard Roche/Ventana SP263 PD-L1 IHC assay used in the AstraZeneca trials and alternative PD-L1 testing methods in urothelial cancer would be conducted in the co-dependent submission based on this application.

24. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

Name of expert 1: **Redacted**

Telephone number(s):

Email address:

Justification of expertise:

Name of expert 2: **Redacted**

Telephone number(s):

Email address:

Justification of expertise:

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

25. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

In Australia in 2013, bladder cancer was the eighth most commonly diagnosed cancer in men, with an incidence of 1957 cases (age-standardised rate 16.5 cases per 100,000) but was much less common in women (incidence of 598 cases and age-standardised rate 4.1 cases per 100,000).[1] In Australia in 2014, mortality from bladder cancer was 735 deaths (age-standardised rate 6.1 deaths per 100,000) and 305 deaths (age-standardised rate 1.9 cases per 100,000) in women.[1] The 5-year relative survival at diagnosis in 2009-2013 was 55.5% in males and 46.1% in females. The 5-year relative survival has slowly declined during the 30 years from 1984-2013.[1]

Bladder cancer is rare under the age of 50 and usually presents in old age. Risk factors for bladder cancer include cigarette smoking, carcinogenic chemical exposure, genetic predisposition and prior radiotherapy/chemoradiation in the pelvis/lower abdomen. More than 90% of bladder cancers form in the lining of the urinary tract (the urothelium) and are known as urothelial carcinomas, or transitional cell carcinomas.[2,3] Urothelial cancers most commonly occur in the bladder, but may also be found in the renal pelvis, ureters and urethra.

Bladder cancer is a highly immunogenic tumour type,[4] consequently immunotherapy treatments for bladder cancer may alter the disease process.

At the initial diagnosis of bladder cancer approximately 70% of cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) and approximately 30% as muscle-invasive bladder cancer (MIBC).[5] Treatment for non-muscle invasive bladder cancer is transurethral resection of the bladder tumour and intravesical chemotherapy or immunotherapy with Bacillus Calmette-Guerin (BCG). Up to 15% of patients diagnosed with non-muscle invasive bladder cancer go on to develop muscle invasive bladder cancer.[6]

Standard treatment for muscle-invasive bladder cancer is radical cystectomy (removal of the bladder), with lymphadenectomy if required, followed by chemotherapy. Cisplatin-containing doublet chemotherapy such as cisplatin/gemcitabine or combination methotrexate, vinblastine, adriamycin and cisplatin (MVAC) are standard treatments in advanced surgically unresectable and metastatic (Stage IV disease) patients able to tolerate cisplatin. Approximately 50% of patients are ineligible for cisplatin treatment,[6] due predominantly to renal dysfunction, poor performance status, or other comorbidities including audiometric hearing loss, peripheral neuropathy and heart failure. Patients unfit for cisplatin-based chemotherapy may be offered a carboplatin-based regimen such as carboplatin/gemcitabine, a single agent taxane or gemcitabine.[6]

This Application proposes durvalumab or durvalumab/tremelimumab as first line treatment for patients with unresectable Stage IV transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder and urethra).

[1] Australian Institute of Health and Welfare (AIHW) Cancer in Australia 2017, p.82-83

[2] Bladder cancer – transitional cell carcinoma Fact Sheet Urological Society of Australia and New Zealand (http://www.usanz.org.au/uploads/65337/ufiles/bladder-cancer.pdf)

[3] Cancer Australia Bladder Cancer https://canceraustralia.gov.au/affected-cancer/cancer-types/bladder-cancer

[4] Schumacher T and Schrieber R. Science 3 April 2015

[5] Babjuk M, Böhle A, Burger M et al. Guidelines on non-muscle-invasive bladder cancer (Ta, T1, and CIS). EAU Guidelines Office, Arnhem, The Netherlands. European Association of Urology; 2014.

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

26. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

A patient suspected of having urothelial cancer may have presented in general practice, or been referred to a urologist for symptoms such as painless haematuria (seen in 80% of patients), dysuria, frequency or urgency.[1] Symptoms of metastatic disease such as bone or flank pain are rare. Medical history, physical examination, and laboratory tests including full blood count and renal function will be carried out. Bladder ultrasonography may also be completed. A diagnosis of urothelial cancer is usually based on cystoscopy and evaluation of the resected tissue.[1] The resected biopsy material is forwarded to a pathology laboratory. Management of urothelial cancer is based on pathological findings from the biopsy, with attention to histology, grade and depth of invasion. The correct staging is determined using computerised tomography (CT) or magnetic resonance imaging (MRI). In patients at high risk of metastases additional tests may be undertaken, such as bone scans and chest imaging.

If the patient has Stage IV disease at diagnosis and is a suitable candidate for systemic treatment then the most appropriate 1st line systemic treatment needs to be determined. These patients are proposed to be eligible for PD-L1 testing to determine the most appropriate 1st line treatment.

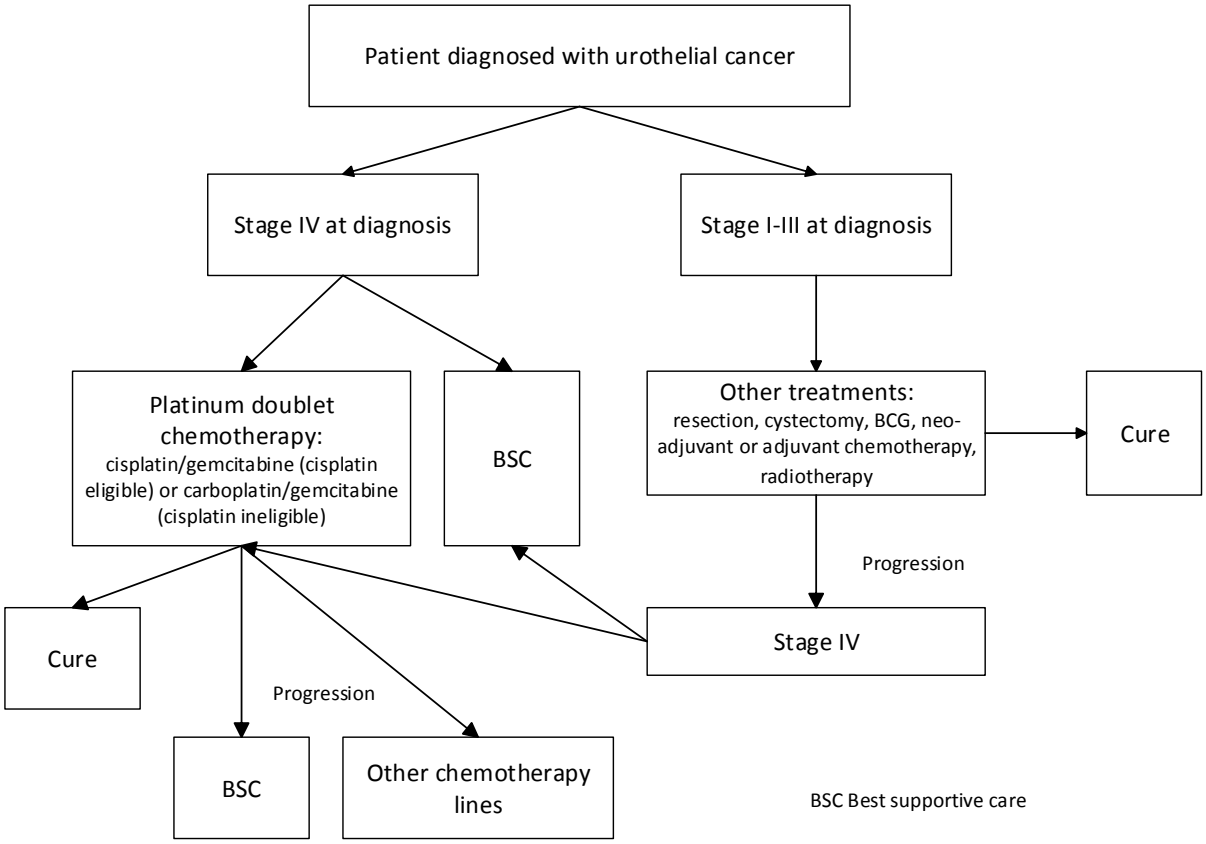
The majority of patients will be diagnosed with earlier stage disease and may undergo other potentially curative treatment options including tumour resection, cystectomy, neo-adjuvant or adjuvant chemotherapy or radiotherapy. Approximately 50% of these patients will eventually relapse to Stage IV disease. At this point, in patients who are suitable candidates for systemic anticancer treatment, it is proposed an additional biopsy would be required to provide tissue for PD-L1 testing in order to determine the most appropriate first line treatment. Use of archived tissue samples from the time of urothelial cancer diagnosis are unlikely to be suitable in most cases as subsequent treatments such as radiotherapy may impact PD-L1 status.

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

27. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

A proportion (approximately 30%) of urothelial cancer patients will be diagnosed with Stage IV disease. The majority of patients will be diagnosed with earlier stage disease and may undergo other potentially curative treatment options including tumour resection, cystectomy, neo-adjuvant or adjuvant chemotherapy or radiotherapy. Approximately 50% of these patients will eventually relapse to Stage IV disease. The proposed medical service would be delivered for patients diagnosed with, or progressing to, Stage IV urothelial cancer, who are eligible candidates for systemic anticancer treatment prior to the selection of 1st line therapy.

Please refer to the Microsoft Visio Attachment to this application, “1LUC Algorithms”, and “Current” drawing for an editable version of the flowchart below.


Patient diagnosed with urothelial cancer
Stage IV at diagnosis
Stage I-III at diagnosis
Platinum doublet chemotherapy: cisplatin/gemcitabine (cisplatin eligible) or carboplatin/gemcitabine (cisplatin ineligible)
BSC
Other treatments: resection, cystectomy, BCG, neo-adjuvant or adjuvant chemotherapy, radiotherapy
Cure
Progression
Stage IV
Cure
Progression
BSC
Other chemotherapy lines
BSC Best supportive care

PART 6b – INFORMATION ABOUT THE INTERVENTION

28. Describe the key components and clinical steps involved in delivering the proposed medical service:

Targeting PD-L1

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. Bladder cancer is a highly immunogenic tumour type, consequently immunotherapy treatments for bladder cancer may alter the disease process.

PD-L1 testing

The level of PD-L1 expression can be assessed using immunohistochemical (IHC) testing with antibodies that bind specifically to the PD-L1 protein.

Tumour biopsy material needs to be sectioned and dried before the IHC staining process. The IHC staining needs to be conducted, interpreted and reported by a professional anatomical pathologist. The test results can then be used to determine 1st line treatment selection.

The evidentiary standard in the AstraZeneca urothelial cancer DANUBE clinical trial is the Roche/Ventana SP263 PD-L1 IHC assay. Roche/Ventana SP263 PD-L1 assay is a sensitive, specific and robust IHC assay for the detection of PD-L1 protein using a rabbit monoclonal primary antibody. This assay has the following specifications:

Tissue: formalin-fixed, paraffin-embedded tissue

Reagents: SP263 (rabbit monoclonal primary antibody); OptiView DAB IHC Detection Kit (indirect, biotin-free system for detection of the rabbit primary antibody)

Instrument/software: BenchMark ULTRA IHC automated slide stainer

The submission will include comparative data on the DANUBE trial based PD-L1 testing method (Roche/Ventana SP263 PD-L1 IHC assay to be registered as a Class 3 IVD in Australia), other commercial PD-L1 test kits available in Australia (such as the DAKO/Agilent Technologies 22C3 PD-L1 pharmDx assay Class 3 IVD), and other published PD-L1 test methods in urothelial cancer.

Durvalumab

Durvalumab (MEDI4736) is a human mAb of the IgG1 kappa subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) to programmed cell death receptor 1 (PD-1). Durvalumab specifically binds human PD-L1. PD-L1 is a member of the B7 family of transmembrane proteins which delivers inhibitory signals to T lymphocytes. It is expressed on various immune cell types and is frequently detected on a broad range of cancer cells. PD-L1 aids cancers in evading detection and elimination by the immune system by repressing the anti-tumour T cell response. Durvalumab prevents PD-L1 from interacting with its receptors, thus relieving its immunosuppressive effects and enhancing the cytotoxic activity of anti-tumour T cells. On May 1, 2017, the U.S. Food and Drug Administration granted accelerated approval to durvalumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Tremelimumab

Tremelimumab (MEDI1123) is a human mAb of the IgG2 kappa subclass which specifically binds to cytotoxic T-lymphocyte antigen -4 (CTLA-4), a cell surface receptor that is expressed exclusively on activated T cells. Upon binding to one of the B7 ligands (CD86 or CD80), CTLA-4 triggers signals that inhibit T cell activity, primarily during the early stages of T cell activation. Tremelimumab blocks the CTLA-4 binding to CD80 and CD86, thereby removing the inhibitory signal induced by CTLA-4, prolonging T cell activation and proliferation and enhancing T cell anti-tumour activity.

Durvalumab/tremelimumab

Targeting both the PD-1 and CTLA-4 pathways may have additive or synergistic activity because the mechanisms of action of the PD-1 and CTLA-4 pathways are non-redundant: whereas PD-1 contributes to

T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation.[1] In addition, CTLA-4 antagonists have been shown to upregulate PD-1 and vice versa, further strengthening the rationale for combination therapy.

This application is a **co-dependent** request for MBS listing of PD-L1 testing to determine which unresectable Stage IV urothelial cancer patients have a high level of PD-L1 gene expression (defined as tumour cells PD-L1 ≥25% or immune cells PD-L1 ≥25%)* in order to qualify for requested PBS access to 1st line durvalumab monotherapy treatment, and which unresectable Stage IV urothelial cancer patients have a low level of PD-L1 gene expression (defined as tumour cells PD-L1 <25% or immune cells PD-L1 <25%)* in order to qualify for requested PBS access to 1st line durvalumab/tremelimumab combination treatment.

*When the immune cell area represents ≤1% of the total tumour area PD-L1 expression is defined as high when baseline tumour expression was tumour cells ≥ 25% and/or immune cells = 100% and PD-L1 low/negative when baseline tumour expression was tumour cells < 25% and immune cells <100%.

[1] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12(4):252-64

29. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

Commercial PD-L1 testing kits such as the Roche/Ventana SP 263 PD-L1 assay and the Agilent Technologies Pty Limited/DAKO PD-L1 22C3 pharmDx assay have registered trademarks. The key component of PD-L1 assays are the different proprietary antibodies used to bind to PD-L1 on tumour tissue in the IHC assay. The antibodies may also have trademarks. Proprietary equipment/software such as the Roche/Ventana BenchMark ULTRA reader and the DAKO readers also have trademarks.

A registered trade mark for durvalumab is being sought. A registered trademark will be sought for tremelimumab.

30. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Yes, inclusion of PD-L1 testing on the MBS to determine eligibility for PBS access to durvalumab or durvalumab/tremelimumab treatment would represent a new approach to unresectable Stage IV urothelial cancer patient management. In alignment with the evidence from the DANUBE trial, patients with unresectable Stage IV urothelial cancer and high (defined as tumour cells ≥ 25% or immune cells ≥ 25%)* levels of PD-L1 expression would be eligible for 1st line PBS durvalumab monotherapy and patients with low (defined as tumour cells < 25% or immune cells < 25%)* levels of PD-L1 expression would be eligible for durvalumab/tremelimumab combination therapy.

Some important differences to MSAC Application 1457/PICO Confirmation 1457 should be noted. In PICO Confirmation 1457 PD-L1 testing is proposed for locally advanced or metastatic urothelial cancer patients who are ineligible for cisplatin-based therapy, whereas the DANUBE trial includes cisplatin eligible as well as ineligible patients. Patients with positive PD-L1 expression (defined as ≥10% combined performance score) receive pembrolizumab 1st line and patients with negative PD-L1 expression (defined as ≥1% and <10% combined performance score) receive carboplatin/gemcitabine as 1st line therapy.

In the current Application it is proposed that PD-L1 testing is used to determine whether durvalumab monotherapy or durvalumab/tremelimumab combination therapy would be the preferred 1st line treatment choice. Platinum-based chemotherapy is displaced to later lines of therapy.

*When the immune cell area represents ≤1% of the total tumour area PD-L1 expression is defined as high when baseline tumour expression was tumour cells ≥ 25% and/or immune cells = 100% and PD-L1 low/negative when baseline tumour expression was tumour cells < 25% and immune cells <100%.

31. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Patients proposed for PD-L1 expression testing would be suitable candidates for systemic anticancer therapy who have been either diagnosed with unresectable Stage IV urothelial cancer, or progressed to Stage IV disease from earlier stage disease. It is expected in the substantial majority of cases that a patient would require PD-L1 testing only once, at the time of Stage IV disease, to determine the

appropriate 1st line treatment choice. For patients diagnosed with unresectable Stage IV disease PD-L1 testing could use tumour material from the same biopsy confirming the urothelial cancer diagnosis. For patients who progress to unresectable Stage IV disease from earlier stage disease, a new biopsy would be required to provide new tissue for PD-L1 testing and determine the most appropriate 1st line treatment. Use of archived tissue from the original urothelial cancer diagnosis is unlikely to be suitable as subsequent therapies (such as radiotherapy) may have altered PD-L1 status.

32. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

For patients diagnosed with unresectable Stage IV urothelial cancer the PD-L1 testing could be done using the tumour material from the same biopsy confirming the urothelial cancer diagnosis, consequently additional services would not be needed in this case. For patients who progress to unresectable Stage IV disease from earlier stage disease, a new biopsy would be required to provide new tissue for PD-L1 testing and determine the most appropriate 1st line treatment.

33. If applicable, advise which health professionals will primarily deliver the proposed service:

PD-L1 testing should be conducted and the results interpreted and reported by suitably qualified and trained anatomical pathologists.

34. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

Not applicable.

35. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

PD-L1 testing to determine 1st line access to durvalumab or durvalumab/tremelimumab should be conducted and reported by suitably qualified and trained anatomical pathologists. The decision to conduct the PD-L1 test should made by the urologist or medical oncologist, with consideration of the staging of the disease, either at the time of diagnosis or after progression from earlier stage disease. The suitability of the patient as a candidate for systemic anticancer treatment must be assessed by the medical oncologist. There may be other relevant tests (eg. renal function tests) that need to be performed or repeated by the urologist or medical oncologist to inform subsequent patient management. PD-L1 testing to determine 1st line treatment should therefore be based on a referral request from a medical oncologist or urologist and should not be pathologist determinable.

36. If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery:

PD-L1 testing should be conducted by suitably qualified professional pathologists who have been trained to conduct immunohistochemical testing specifically for PD-L1 following Australian national accreditation standards (NATA accreditation). A Quality Assurance Program conducted by the Royal College of Pathologists of (RCPA) would also enhance the service delivery.

37. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

- ☐ Inpatient private hospital
- ☐ Inpatient public hospital
- ☐ Outpatient clinic
- ☐ Emergency Department
- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Residential aged care facility
- ☐ Patient's home
- ☒ Laboratory
- ☐ Other – please specify below

The medical service will be conducted in pathology laboratories which may be private companies, or may be domiciled within private or public research institutes or hospitals.

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

Not applicable.

38. Is the proposed medical service intended to be entirely rendered in Australia?

☒ Yes
☐ No – please specify below

Specify further details here. Not applicable

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

39. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

The comparator for PD-L1 testing in Stage IV urothelial cancer to determine 1st line treatment is no PD-L1 testing, as IHC testing for PD-L1 expression in urothelial cancer patients is not currently carried out as a standard laboratory procedure in Australia.

The comparator for 1st line durvalumab monotherapy or durvalumab/tremelimumab combination treatment in urothelial cancer patients is currently 1st line platinum-based chemotherapy. The preferred platinum doublet regimen will depend on whether the patient can tolerate cisplatin treatment or not. Cisplatin/gemcitabine is the most commonly used regimen, although a small proportion of patients may receive MVAC (methotrexate, vinblastine, adriamycin and cisplatin).[1,2] In approximately 50% of patients unable to tolerate cisplatin-based regimens because of impaired renal function or significant co-morbidities carboplatin/gemcitabine is the preferred regimen.

The DANUBE study population comprises Stage IV urothelial cancer patients, and it is this patient group who are the proposed candidates for PD-L1 testing to determine access to durvalumab or durvalumab/tremelimumab treatment.

A future comparator for durvalumab monotherapy treatment could be 1st line pembrolizumab monotherapy treatment in patients who have a high level of PD-L1 expression and are ineligible for cisplatin treatment (refer MSAC PICO Confirmation 1457). A comparison of durvalumab to pembrolizumab will be included in a submission based on this application. It should be noted that the first line durvalumab treatment arm of the DANUBE study includes both cisplatin-eligible and cisplatin-ineligible patients, whereas the pembrolizumab trial includes only cisplatin ineligible patients.

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

[2] Australian clinical expert opinion (AstraZeneca Bladder Cancer Advisory Board)

40. Does the medical service that has been nominated as the comparator have an existing MBS item number(s)?

☐ Yes (please provide all relevant MBS item numbers below)
☒ No

Specify item number/s here:

IHC testing for PD-L1 expression is not currently listed as an MBS item for any tumour type. PD-L1 testing to determine access to pembrolizumab in cisplatin-ineligible locally advanced or metastatic urothelial cancer patients may be listed on the MBS in the future as an outcome of MSAC PICO Confirmation 1457. Other forms of IHC testing (not specific for PD-L1) are listed as MBS items.

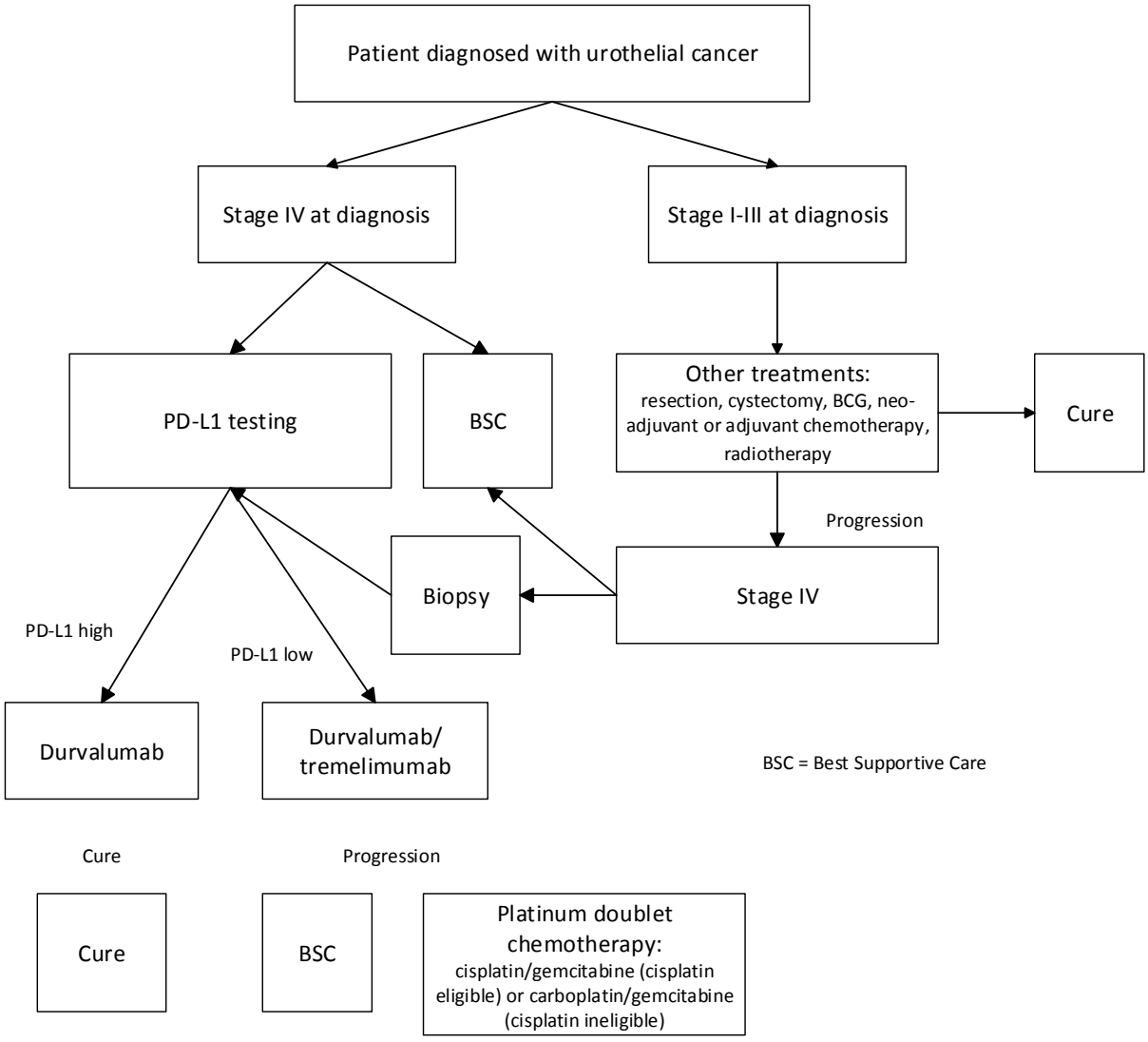
41. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):

A proportion (approximately 30%) of urothelial cancer patients will be diagnosed with Stage IV disease. For patients with Stage IV disease about 80% will be suitable candidates for 1st line systemic treatment, and 20% would receive best supportive care only. The majority of patients will be diagnosed with earlier stage disease and may undergo other potentially curative treatment options including tumour resection, cystectomy, neo-adjuvant or adjuvant chemotherapy or radiotherapy. Approximately 50% of these patients will eventually progress to Stage IV disease. The standard of care 1st line treatment for patients with Stage IV urothelial cancer is currently a platinum doublet such as cisplatin/gemcitabine (for patients who are eligible for cisplatin) or carboplatin/gemcitabine (for cisplatin-ineligible patients). A small proportion (approximately 10%) of patients who receive 1st line chemotherapy may not experience further

progression of disease ("cure")[1], however the majority of patients eventually progress and receive best supportive care only or subsequent lines of chemotherapy.

[1]Australian clinical expert opinion (AstraZeneca Bladder Cancer Advisory Board)

Please refer to the Microsoft Visio Attachment to this application, "1LUC Algorithms", and "Proposed" drawing for an editable version of the flowchart below.



42. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

☒ Yes
☐ No

The proposed medical service (PD-L1 expression testing) will be used instead of the comparator (no testing). The proposed 1st line treatments durvalumab monotherapy or durvalumab/tremelimumab combination therapy would be used instead of 1st line platinum-based chemotherapy. Platinum-based chemotherapy would be displaced as the 1st line preferred treatment, however it would remain an option for subsequent treatment lines.
For the comparison of durvalumab and pembrolizumab monotherapy, durvalumab would be used instead of pembrolizumab in a proportion of patients.

(b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:

Up to 100% substitution of no testing with PD-L1 testing. Up to 100% substitution of platinum-based chemotherapy with durvalumab or durvalumab/tremelimumab. Durvalumab could be used instead of pembrolizumab in a proportion of patients.

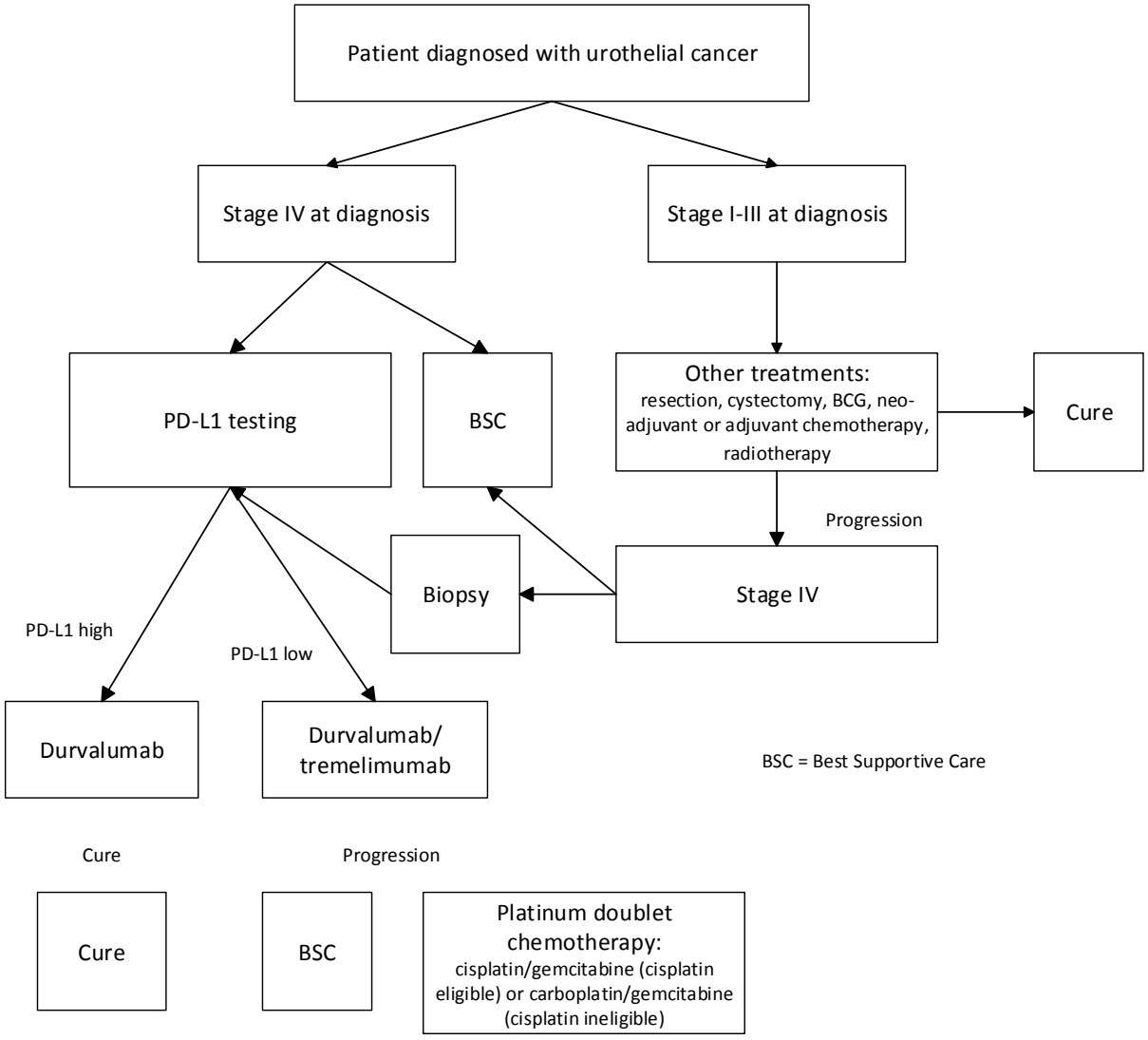
43. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):

A proportion (approximately 30%) of urothelial cancer patients will be diagnosed with Stage IV disease. PD-L1 testing is proposed in patients who have Stage IV disease at the time of diagnosis if the patient is a suitable candidate for systemic anticancer treatment.

The majority of patients will be diagnosed with earlier stage disease. PD-L1 testing is not proposed for patients diagnosed with earlier stage disease as other potentially curative treatment options are preferred, such as resection of the tumour, BCG treatment, cystectomy, neo-adjuvant or adjuvant chemotherapy or radiotherapy. Some of these treatment options are also known to affect PD-L1 status so testing PD-L1 status in earlier stage disease is not appropriate. However, approximately 50% of these patients will eventually progress to Stage IV disease. For patients who progress to Stage IV disease about 80% will be suitable candidates for 1st line systemic treatment, and 20% would receive best supportive care only. PD-L1 testing is also proposed for patients who progress to Stage IV from earlier stage disease and are suitable candidates for 1st line systemic treatment. Another biopsy to obtain tissue for PD-L1 testing at the time of progression to Stage IV would be required in these patients. It is proposed that patients with high levels of PD-L1 expression (tumour cells ≥ 25% or immune cells ≥ 25%)* would receive durvalumab monotherapy and patients with low levels of PD-L1 expression (tumour cells < 25% or immune cells < 25%)* would receive combination therapy with durvalumab/tremelimumab. A proportion of patients may not experience further progression of disease (“cure”). The majority of patients will eventually progress and receive best supportive care only or platinum doublet chemotherapy.

*When the immune cell area represents ≤1% of the total tumour area PD-L1 expression is defined as high when baseline tumour expression was tumour cells ≥ 25% and/or immune cells = 100% and PD-L1 low/negative when baseline tumour expression was tumour cells < 25% and immune cells <100%.

Please refer to the Microsoft Visio Attachment to this application, 1LUC Algorithms, and “Proposed” drawing for an editable version of the flowchart below.


Patient diagnosed with urothelial cancer
Stage IV at diagnosis
Stage I-III at diagnosis
PD-L1 testing
BSC
Other treatments:
resection, cystectomy, BCG, neo-adjuvant or adjuvant chemotherapy, radiotherapy
Cure
Progression
Biopsy
Stage IV
PD-L1 high
PD-L1 low
Durvalumab
Durvalumab/ tremelimumab
BSC = Best Supportive Care
Cure
Progression
Cure
BSC
Platinum doublet chemotherapy:
cisplatin/gemcitabine (cisplatin eligible) or carboplatin/gemcitabine (cisplatin ineligible)

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

PD-L1 expression testing of unresectable Stage IV urothelial cancer patients and 1st line treatment with durvalumab monotherapy in patients with high PD-L1 expression (tumour cells ≥ 25% or immune cells ≥ 25%) or durvalumab/tremelimumab combination therapy in patients with low PD-L1 expression (tumour cells < 25% or immune cells < 25%) is **superior** to no PD-L1 testing of Stage IV urothelial cancer patients and standard of care treatment (platinum doublet chemotherapy).

For the comparison of durvalumab with pembrolizumab in patients who have a high level of PD-L1 expression the clinical claim is **non-inferiority**.

45. Please advise if the overall clinical claim is for:

☒ Superiority
☐ Non-inferiority

46. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

Safety and tolerability of durvalumab monotherapy and durvalumab/tremelimumab combination therapy treatment assessed by adverse events (AEs), physical examinations, laboratory findings, and vital signs

Adverse events associated with re-biopsy

Clinical Effectiveness Outcomes:

Test outcomes

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

Sensitivity

Specificity

Positive predictive value

Negative predictive value

Receiver operator characteristic (ROC)

Comparative performance of PD-L1 testing methods:

Concordance with other commercially available PD-L1 antibodies

Concordance with other commercially available PD-L1 assays

Prevalence of PD-L1 expression assessed using different antibodies/assays

Re-testing rates

Clinical utility of test:

Efficacy and safety outcomes of durvalumab and durvalumab/tremelimumab treatment with or without PD-L1 testing

Other test-related considerations:

Re-biopsy rates

Test turn-around time

Estimated number of patients being tested

Number of patients tested per case of PD-L1 high and PD-L1 low result detected

Number of patients tested per case of PD-L1 high treated with durvalumab and PD-L1 low treated with durvalumab/tremelimumab

Cost of testing per case of PD-L1 high and PD-L1 low result detected

Cost of testing per case of PD-L1 high treated with durvalumab and PD-L1 low treated with durvalumab/tremelimumab

Drug outcomes

Clinical efficacy of durvalumab and durvalumab/tremelimumab:

Co-primary outcomes:

Overall survival (OS)

Progression-free survival (PFS, blinded independent central review (BICR), RECIST v1.1 criteria)

Secondary outcomes:

Objective response rates (ORR)

Duration of response (DoR)

Disease control rate (DCR)

Proportion of patients alive and progression free at 12 months from randomization (APF12)

Overall survival for 24 months (OS24)

Health-related quality of life in urothelial cancer patients using the FACT-BL questionnaire (derived NFBlSI-18 score, FACT-BL TOI, and FACT-BL Total score)

Time to second progression (PFS2)

Exploratory outcomes:

Health state utility (EQ-5D-5L)

PFS, APF12, ORR, DoR, and DCR using BICR assessment according to irRECIST

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

47. Estimate the prevalence and/or incidence of the proposed population:

The estimated incidence of bladder cancer in 2017 is 2,995 cases (2267 males and 728 females).[1] The 1-year prevalence of bladder cancer (based on latest data from 2012) is 2131 persons (1671 males and 460 females). The proportion of bladder cancer patients with urothelial (transitional cell) carcinoma is 90%.[2,3]

The proportion of patients with unresectable Stage IV (metastatic) disease at diagnosis has been estimated at 32.4% (Western Europe, 2013) and 28.7% (United States, 2014). Approximately 30% will be used to estimate the population who are Stage IV at diagnosis.

The proportion of patients relapsing to Stage IV disease from earlier stage disease has been estimated at 50%.[5]

Approximately 20% of patients with Stage IV disease are not suitable candidates for systemic chemotherapy treatment and receive best supportive care only.[5] The remaining 80% of Stage IV patients are suitable candidates for first line chemotherapy.[5]

Incident patients with urothelial carcinoma	2696
Prevalent patients with urothelial carcinoma	1918
Incident urothelial carcinoma patients Stage IV at diagnosis	809
Prevalent patients with urothelial carcinoma progressing to Stage IV from earlier stage disease	960
All urothelial carcinoma patients Stage IV and suitable for systemic first line treatment	1415

[1] Australian Institute of Health and Welfare (AIHW) Cancer in Australia 2017, p.82-83

[2] Bladder cancer – transitional cell carcinoma Fact Sheet Urological Society of Australia and New Zealand (http://www.usanz.org.au/uploads/65337/ufiles/bladder-cancer.pdf)

[3] Cancer Australia Bladder Cancer https://canceraustralia.gov.au/affected-cancer/cancer-types/bladder-cancer

[4] Kantar Health physician survey 2013, 2014

[5] Australian clinical expert opinion (AstraZeneca Bladder Cancer Advisory Board)

48. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

It is proposed that PD-L1 testing would be conducted only once in most cases. In patients diagnosed with Stage IV disease PD-L1 testing could be done prior to initiation of 1st line treatment using the same biopsy material used to confirm urothelial cancer. According to the estimates in Question 47 above, approximately 809 patients could be Stage IV at the time of diagnosis, however only around 647 patients would be suitable candidates for systemic 1st line treatment and should have PD-L1 testing.

The majority of patients will be diagnosed with earlier stage disease and may undergo other treatment options including cystectomy, neo-adjuvant or adjuvant chemotherapy with or without radiotherapy. Some of these treatments impact PD-L1 status. Approximately half of these patients will eventually progress to Stage IV disease. According to the estimates in Question 47 above, approximately 960 patients per year could progress to Stage IV from earlier stage disease and of these approximately 768

would be suitable for systemic 1st line treatment. Re-biopsy would be required to obtain tissue for PD-L1 testing in these patients.

In total approximately 1415 urothelial cancer patients per year could receive PD-L1 testing.

49. How many years would the proposed medical service(s) be required for the patient?

PD-L1 testing is not required for routine monitoring of a patient. It is proposed that the substantial majority of patients will only require PD-L1 testing once.

50. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

In total approximately 1415 urothelial cancer patients per year could receive PD-L1 testing and they would be tested only once, consequently the projected number of patients who would utilise PD-L1 testing in the first full year would also be 1415.

51. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

PD-L1 testing is not expected to experience significant constraints in supply and demand over the first 3 years of listing. There are no anticipated constraints in the supply of commercial PD-L1 testing kits for urothelial cancer. It is also anticipated in-house PD-L1 test methods would develop over the 1-3 year timeframe, in particular at major hospital pathology laboratories with research capabilities. Over this time frame PD-L1 testing may be sought for other indications/tumour types to determine access to PBS treatments. In order to reduce the risk of leakage to other populations it is proposed that the MBS restriction should specify PD-L1 testing of tumour material (tumour cells and immune cells) from patients with a urothelial cancer diagnosis. This will be clarified in the co-dependent PBS criteria, however the additional clarification in the MBS criteria would reduce the risk of leakage in populations where the clinical and cost effectiveness of PD-L1 testing has not yet been determined.

PART 8 – COST INFORMATION

52. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

The proposed fee for a single antibody PD-L1 test on the MBS is yet to be clarified but is expected to be similar to other MBS items for IHC testing.

53. Specify how long the proposed medical service typically takes to perform:

IHC testing for PD-L1 expression has been estimated to take between 2.5-4 hours to perform depending on instrumentation and protocol being followed.

54. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

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

PART 9 – FEEDBACK

The Department is interested in your feedback.

55. How long did it take to complete the Application Form?

Redacted

56. (a) Was the Application Form clear and easy to complete?

☐ Yes
☐ No

(b) If no, provide areas of concern:

Redacted

57. (a) Are the associated Guidelines to the Application Form useful?

☐ Yes
☐ No

Redacted

(b) If no, what areas did you find not to be useful?

Insert feedback here

58. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

☐ Yes
☐ No

(b) If yes, please advise:

Redacted